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The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

02017586.5

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk



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Aventis Pharma Deutschland GmbH
Brüningstrasse 50
65929 Frankfurt am Main
ALLEMAGNE

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(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se référer à la description.)

Acylated, heteroaryl-condensed cycloalkenylamines and their use as
pharmaceuticals

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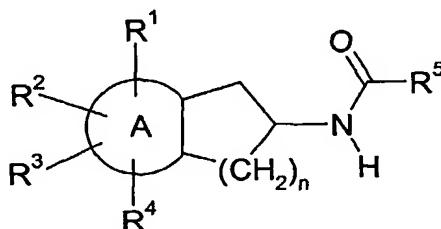
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Acylated, heteroaryl-condensed cycloalkenylamines and their use as
pharmaceuticals

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The present invention relates to acylated, heteroaryl-condensed cycloalkenylamines
of the formula I,



I

10

in which A, R¹, R², R³, R⁴, R⁵ and n have the meanings indicated below. The
compounds of formula I are valuable pharmaceutically active compounds which are
useful in the treatment of various disease states including cardiovascular disorders
such as atherosclerosis, thrombosis, coronary artery disease, hypertension and
cardiac insufficiency. They upregulate the expression of the enzyme endothelial nitric
oxide (NO) synthase and can be applied in conditions in which an increased
expression of said enzyme or an increased NO level or the normalization of a
decreased NO level is desired. The invention furthermore relates to processes for the
preparation of compounds of the formula I, their use, in particular as active
ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.

20

Endothelial NO synthase (eNOS, NOS-III) belongs to a group of three isoenzymes
which produce nitric oxide (NO) by oxidation of arginine. Endothelially released NO is
of central importance in a number of key cardiovascular mechanisms. It has a
vasodilating effect and inhibits the aggregation of platelets, the adhesion of
leukocytes to the endothelium and the proliferation of intimal smooth muscle cells.

25

Endothelial NO synthase is subject to physiological and pathophysiological regulation both at the transcriptional and at the post-transcriptional level. Enzyme already present in the endothelium may undergo calcium-dependent and calcium-independent activation through phosphorylation of specific amino acids, but also by
5 direct interactions with specific proteins. Stimulators of this, usually transient, NO release are, extracellular arginine, 17β -estrogen and the mechanical stimulus exerted on the luminal surface of the endothelium by the blood flow (shear stress). The latter additionally leads to regulation of eNOS at the transcriptional level. Thus, for example, Sessa et al. (Circ. Research 74 (1994) 349) were able by means of
10 exercise training and the increase in shear stress associated therewith to obtain a marked increase in eNOS.

Whether regulation at the post-transcriptional level is relevant in vivo, is often not unambiguously proved. Thus, for example, administration of a high arginine dose is
15 followed by only a transient improvement in the endothelium-dependent vasorelaxation in patients with coronary heart disease.

On the other hand, the significance of the upregulation of the eNOS protein is scientifically accepted. Thus, there are findings which show that the protective
20 properties of the HMG-CoA reductase inhibitor simvastatin can be attributed, besides the lipid lowering effect, also in part to an increase in eNOS expression in vivo (Endres et al., Proc. Natl. Acad. Sci. USA 95 (1998) 8880). It is additionally known that single point mutations in the 5'-flanking region of the eNOS gene ("eNOS promoter"), and the reduction in the rate of eNOS gene transcription associated
25 therewith, in the Japanese population is associated with an increase in the risk of coronary spasms (Nakayama et al., Circulation 99 (1999) 2864).

The current assumption therefore is that the transcriptional and post-transcriptional mechanisms of eNOS regulation are seriously disturbed in a large number of
30 disorders, especially in cardiovascular disorders. Even in very early stages of a wide variety of cardiovascular disorders it is possible for a dysfunction of this type in the endothelium lining the blood vessels to lead to a deficiency of bioactive NO, which is

manifested as the disorder progresses in the form of measurable pathophysiological and morphological changes. Thus, critical steps in early atherogenesis are speeded up by a decrease in endothelial NO release, such as, for example, the oxidation of low density lipoproteins, the recruitment and deposition of monocytes in the intima of vessels, and the proliferation of intimal cells. A consequence of atherogenesis is the formation of plaques on the inside of the blood vessels, which may in turn lead, through a diminution in the shear stress, to a further decrease in endothelial NO release and a further deterioration in the pathology. Since endothelial NO is also a vasodilator, a decrease thereof frequently also leads to hypertension, which may, as an independent risk factor, cause further organ damage.

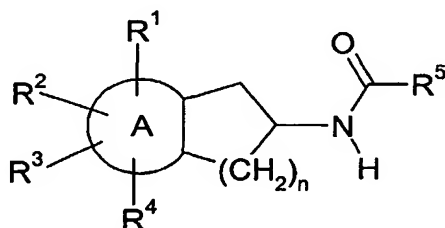
The aim of a therapeutic approach to the treatment of these disorders must accordingly be to interrupt this chain of events by increasing the endothelial NO expression. Gene transfer experiments which lead in vitro to overexpression of NO synthase in previously damaged vessels are in fact able to counteract the described processes and are thus evidence of the correctness of this approach (Varenne et al., Hum. Gene Ther. 11 (2000) 1329).

Some low molecular weight compounds which, in cell cultures, may lead to a direct effect on eNOS transcription and expression are disclosed in the literature. The statins which have already been mentioned are, however, the only substances for which it has been possible to date to show such an increase in eNOS in vivo as a side effect. But in view of the known range of side effects of this class of substances it is unclear how far this effect is present in a toxicologically unproblematic dose.

Liao et al. claim in WO 99/47153 and WO 00/03746 the use of rhoGTPase inhibitors and agents which influence the organization of the actin cytoskeleton for increasing eNOS in endothelial cells and for the therapy of various disorders such as, for example, stroke or pulmonary hypertension without, however, indicating a specific way of achieving this.

International patent applications PCT/EP02/01443, PCT/EP02/01444, PCT/EP02/01448 and PCT/EP02/01449 disclose acylated, benzo-condensed cycloalkenylamines which upregulate eNOS expression in endothelial cells and are useful pharmaceutically active ingredients for the treatment of various diseases, but there is an ongoing need for further eNOS expression enhancers with a favorable property profile. The present invention satisfies this need by providing the compounds of the formula I and methods of using them.

The present invention relates to acylated, heteroaryl-condensed cycloalkenylamines of the formula I,



in any of their stereoisomeric forms and mixtures thereof in any ratio, and the pharmaceutically acceptable salts thereof, wherein in the formula I:

the ring A, which comprises the two carbon atoms common to the ring A and the cycloalkenyl ring in formula I, is an aromatic 5-membered or 6-membered ring containing 1 or 2 nitrogen atoms as ring heteroatoms, or an aromatic 5-membered ring containing 1 ring heteroatom which is an oxygen atom or a sulfur atom or 2 ring heteroatoms one of which is a nitrogen atom and the other of which is an oxygen atom or a sulfur atom;

R^1 and R^4 are independently from each other selected from the group consisting of: H; unsubstituted and at least monosubstituted C_1 - C_{10} -alkyl, C_2 - C_{10} -alkenyl and C_2 - C_{10} -alkynyl, the substituents of which are selected from the group consisting of F, OH, C_1 - C_8 -alkoxy, C_1 - C_8 -alkylmercapto, -CN, $COOR^6$, $CONR^7R^8$, and unsubstituted and at least monosubstituted phenyl and heteroaryl where the substituents of the

phenyl and heteroaryl groups are selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃; unsubstituted and at least monosubstituted phenyl and heteroaryl the substituents of which are selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃; COR⁹; CONR¹⁰R¹¹; 5 COOR¹²; CF₃; halogens; -CN; NR¹³R¹⁴; OR¹⁵; S(O)_mR¹⁶; SO₂NR¹⁷R¹⁸; and NO₂; but cannot be halogen, -CN or NO₂ if R¹ or R⁴ is bonded to a ring nitrogen atom;

R² and R³ are independently from each other selected from the group consisting of: H; halogens; -CN; unsubstituted and at least monosubstituted C₁-C₁₀-alkyl the 10 substituents of which are selected from the group consisting of OH, phenyl, and heteroaryl; OH; C₁-C₁₀-alkoxy; phenoxy; S(O)_mR¹⁹; CF₃; -CN; NO₂; C₁-C₁₀-alkylamino; di(C₁-C₁₀-alkyl)amino; (C₁-C₆-alkyl)-CONH-; unsubstituted and at least monosubstituted phenyl-CONH- and phenyl-SO₂-O- the substituents of which are selected from the group consisting of halogens, -CN, methyl and methoxy; C₁-C₆- 15 alkyl-SO₂-O-; unsubstituted and at least monosubstituted (C₁-C₆-alkyl)-CO- the substituents of which are selected from the group consisting of F, di(C₁-C₃-alkyl)amino, pyrrolidinyl and piperidinyl; and phenyl-CO- the phenyl part of which is unsubstituted or at least monosubstituted by substituents selected from the group consisting of C₁-C₃-alkyl, halogens and methoxy; but cannot be halogen, -CN or NO₂ 20 if R² or R³ is bonded to a ring nitrogen atom;

where, if A is a 6-membered aromatic ring, 2 or 3 of the groups R¹, R², R³ and R⁴ are present and are bonded to the carbon atoms in the ring A which are not shared with the cycloalkenyl ring, and, if A is a 5-membered aromatic ring, 1, 2 or 3 of the groups 25 R¹, R², R³ and R⁴ are present and are bonded to the carbon atoms in the ring A which are not shared with the cycloalkenyl ring and, in the case of a pyrrole, pyrazole or imidazole ring, to 1 ring nitrogen atom;

R⁵ is a group Ar or a group Hetar both of which are unsubstituted or carry one or 30 more identical or different substituents selected from the group consisting of: halogens; -CN; NH₂; unsubstituted and at least monosubstituted C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl, C₂-C₁₀-alkynyl, C₁-C₁₀-alkoxy, C₁-C₁₀-alkylamino and di(C₁-C₁₀-alkyl)amino,

- the substituents of which are selected from the group consisting of F, OH, C₁-C₈-alkoxy, aryloxy, C₁-C₈-alkylmercapto, NH₂, C₁-C₈-alkylamino and di(C₁-C₈-alkyl)amino; C₃-C₅-alkandiyl; phenyl; heteroaryl; aryl-substituted or heteroaryl-substituted C₁-C₄-alkyl; CF₃; NO₂; OH; phenoxy; benzyloxy; (C₁-C₁₀-alkyl)-COO-;
- 5 S(O)_mR²⁰; SH; phenylamino; benzylamino; (C₁-C₁₀-alkyl)-CONH-; (C₁-C₁₀-alkyl)-CO-N(C₁-C₄-alkyl)-; phenyl-CONH-; phenyl-CO-N(C₁-C₄-alkyl)-; heteroaryl-CONH-; heteroaryl-CO-N(C₁-C₄-alkyl)-; (C₁-C₁₀-alkyl)-CO-; phenyl-CO-; heteroaryl-CO-; CF₃-CO-; -OCH₂O-; -OCF₂O-; -OCH₂CH₂O-; -CH₂CH₂O-; COOR²¹; CONR²²R²³; C(NH)-NH₂; SO₂NR²⁴R²⁵; R²⁶SO₂NH-; R²⁷SO₂N(C₁-C₆-alkyl)-; and a residue of a
- 10 saturated or at least monounsaturated aliphatic, monocyclic 5-membered to 7-membered heterocycle containing 1, 2 or 3 heteroatoms selected from the group consisting of N, O and S, which heterocycle can be substituted by one or more substituents selected from the group consisting of halogens, C₁-C₃-alkyl, C₁-C₃-alkoxy, OH, oxo and CF₃, where said heterocycle can optionally be condensed to the
- 15 said group Ar or the said group Hetar; wherein all aryl, heteroaryl, phenyl, aryl-containing, heteroaryl-containing and phenyl-containing groups, which are optionally present in the said substituents of the said group Ar or the said group Hetar, can be substituted by one or more substituents selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, OH, C₁-C₃-alkoxy, and CF₃;

20

R⁶ is selected from the group consisting of:

- H; C₁-C₁₀-alkyl which can be substituted by one or more substituents selected from the group consisting of F, C₁-C₈-alkoxy and di(C₁-C₈-alkyl)amino; aryl-(C₁-C₄-alkyl)- and heteroaryl-(C₁-C₄-alkyl)- both of which can be substituted by one or more
- 25 substituents selected from the group consisting of halogens, C₁-C₄-alkyl, C₁-C₄-alkoxy and di(C₁-C₆-alkyl)amino;

R⁷ is selected from the group consisting of:

- H; C₁-C₁₀-alkyl which can be substituted by one or more substituents selected from the group consisting of F, C₁-C₈-alkoxy, di(C₁-C₈-alkyl)amino and phenyl; phenyl;
- 30 indanyl; and heteroaryl; wherein each of the aromatic groups can be unsubstituted or

carry one or more substituents selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃;

R⁸ is H or C₁-C₁₀-alkyl;

5

R⁹ is selected from the group consisting of:

C₁-C₁₀-alkyl which can be substituted by one or more substituents from the group consisting of F, C₁-C₄-alkoxy and di(C₁-C₃-alkyl)amino; and unsubstituted and at least monosubstituted phenyl and heteroaryl the substituents of which are selected

10 from the group consisting of C₁-C₃-alkyl, C₁-C₃-alkoxy, halogens, -CN and CF₃;

R¹⁰, independently from R⁷, is defined as R⁷;

R¹¹, independently from R⁸, is defined as R⁸;

15

R¹², independently from R⁶, is defined as R⁶;

R¹³ is selected from the group consisting of:

H; C₁-C₆-alkyl; unsubstituted and substituted phenyl, benzyl, heteroaryl, (C₁-C₆-alkyl)-CO-, phenyl-CO-, and heteroaryl-CO-, the substituents of which are selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃, wherein one or more of these substituents can be present;

20

R¹⁴, independently from R¹³, is defined as R¹³;

25

R¹⁵ is selected from the group consisting of:

H; C₁-C₁₀-alkyl; (C₁-C₃-alkoxy)-C₁-C₃-alkyl- and substituted and unsubstituted benzyl, phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃, wherein one or more

30

R¹⁶ is selected from the group consisting of:

C₁-C₁₀-alkyl which can be substituted by one or more substituents selected from the group consisting of F, OH, C₁-C₈-alkoxy, aryloxy, C₁-C₈-alkylmercapto, C₁-C₈-alkylamino and di(C₁-C₈-alkyl)amino; CF₃; and substituted and unsubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of
5 halogens, -CN, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃, wherein one or more of these substitutents can be present;

R¹⁷, independently from R⁷, is defined as R⁷;

10 R¹⁸, independently from R⁸, is defined as R⁸;

R¹⁹, independently from R¹⁶, is defined as R¹⁶;

R²⁰, independently from R¹⁶, is defined as R¹⁶;

15 R²¹, independently from R⁶, is defined as R⁶;

R²², independently from R⁷, is defined as R⁷;

20 R²³, independently from R⁸, is defined as R⁸;

R²⁴, independently from R⁷, is defined as R⁷;

R²⁵, independently from R⁸, is defined as R⁸;

25 R²⁶, independently from R¹⁶, is defined as R¹⁶;

R²⁷, independently from R¹⁶, is defined as R¹⁶;

30 heteroaryl is a residue of a 5-membered to 10-membered, aromatic, monocyclic or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S;

the group Hetar is a residue of a 5-membered to 10-membered, aromatic, monocyclic or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S;

5

aryl is phenyl, naphth-1-yl or naphth-2-yl;

the group Ar is phenyl, naphth-1-yl or naphth-2-yl;

10 m is 0, 1 or 2;

n is 1, 2 or 3.

If groups or substituents in the compounds of the formula I such as, for example, aryl, heteroaryl, alkyl etc., can be present several times, they all independently from each other have the meanings indicated and can hence, in each individual case, be identical with or different from each other. An example is the di(C₁-C₁₀-alkyl)amino group in which the alkyl substituents can be identical or different.

Alkyl, alkenyl and alkynyl residues can be linear or branched, acyclic or cyclic. This also applies when they are part of other groups, for example alkoxy groups, alkoxy carbonyl groups or substituted amino groups, or when they are substituted.

Examples of alkyl groups are methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, the n-isomers of these residues, isopropyl, isobutyl, isopentyl, sec-butyl, tert-butyl, neopentyl, 3,3-dimethylbutyl. The term alkyl here also expressly includes cycloalkyl groups and cycloalkyl-alkyl- groups (i. e., alkyl substituted by cycloalkyl) which groups contain at least three carbon atoms. Examples of such cycloalkyl residues are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl. All cycloalkyl groups can be substituted by one or more identical or different C₁-C₄-alkyl residues, in particular by methyl. Examples of substituted cycloalkyl residues are 4-methylcyclohexyl, 4-tert-butylcyclohexyl or 2,3-

dimethylcyclopentyl. Furthermore, unless stated otherwise, the term alkyl here also includes unsubstituted alkyl residues as well as alkyl residues which are substituted by one or more, for example 1, 2, 3 or 4, identical or different residues, for example aryl groups. In substituted alkyl residues, for example arylalkyl-, hydroxyalkyl- such as hydroxy-(C₁-C₃)-alkyl- or alkoxyalkyl- such as C₁-C₄-alkyl-O-(C₁-C₃)-alkyl-, the substituents can be present in any desired position.

Examples of alkenyl and alkynyl groups are vinyl, 1-propenyl, 2-propenyl (i.e. allyl), 2-butenyl, 2-methyl-2-propenyl, 3-methyl-2-butenyl, ethynyl, 2-propynyl (i.e. propargyl), 2-butyne or 3-butyne. The term alkenyl here also expressly includes cycloalkenyl groups and cycloalkenyl-alkyl- groups (i.e. alkyl substituted by cycloalkenyl) which groups contain at least three carbon atoms. Examples of cycloalkenyl residues are cyclopentenyl, cyclohexenyl, cycloheptenyl and cyclooctenyl. All cycloalkenyl groups can be substituted by one or more identical or different C₁-C₄-alkyl residues, in particular by methyl. Furthermore, unless stated otherwise, the term alkenyl and alkynyl here also includes unsubstituted alkenyl and alkynyl residues as well as alkenyl and alkynyl residues which are substituted by one or more, for example 1, 2, 3 or 4, identical or different residues, for example aryl groups. In substituted alkenyl and alkynyl residues, for example arylalkenyl-, hydroxyalkenyl- such as hydroxy-(C₂-C₃)-alkenyl- or alkoxyalkenyl- such as C₁-C₃-alkyl-O-(C₂-C₄-alkenyl)-, the substituents can be present in any desired position.

Examples of C₃-C₅-alkandiyl are -CH₂CH₂CH₂-, -CH₂-CH(CH₃)-, -CH₂CH₂CH₂CH₂- and -CH₂CH₂CH₂CH₂CH₂- groups.

If not stated otherwise, the above-mentioned phenyl residues, naphthyl and indanyl residues and heterocyclic residues (including heteroaryl residues) can be unsubstituted or can carry one or more, for example 1, 2, 3 or 4, of the substituents indicated in the above definition which substituents can be present in any desired position. If in compounds of the formula I nitro groups are present as substituents, in a preferred embodiment of the invention in total only up to two nitro groups are present in the molecule. In monosubstituted phenyl residues the substituent can be in

the 2-position, the 3-position or the 4-position, in disubstituted phenyl residues the substituents can be in 2,3-position, 2,4-position, 2,5-position, 2,6-position, 3,4-position or 3,5-position. In trisubstituted phenyl residues the substituents can be in 2,3,4-position, 2,3,5-position, 2,3,6-position, 2,4,5-position, 2,4,6-position or 3,4,5-
 5 position. In fourfold substituted phenyl residues, the substituents can be in the 2,3,4,5-position, the 2,3,4,6-position, or the 2,3,5,6-position. Toly (= methylphenyl) can be 2-tolyl, 3-tolyl or 4-tolyl. Naphthyl can be 1-naphthyl or 2-naphthyl. In monosubstituted 1-naphthyl residues the substituent can be in the 2-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position,
 10 in monosubstituted 2-naphthyl residues in the 1-position, the 3-position, the 4-position, the 5-position, the 6-position, the 7-position or the 8-position. In higher substituted naphthyl residues, for example 1-naphthyl residues or 2-naphthyl residues which carry two or three substituents, the substituents can be present in any desired positions. Indanyl residues include indan-1-yl residues and indan-2-yl
 15 residues which can be unsubstituted or carry one or more of the substituents indicated. In case the indanyl residues are substituted, the substituent or substituents can be present in any of the positions possible.

Unless stated otherwise, heteroaryl residues and heterocyclic residues are preferably
 20 derived from heterocycles which contain 1, 2, 3 or 4 heteroatoms which can be identical or different; more preferably they are derived from heterocycles which contain 1, 2 or 3, in particular 1 or 2, heteroatoms which can be identical or different. Unless stated otherwise, the heterocycles can be monocyclic or polycyclic, for example monocyclic, bicyclic or tricyclic. Preferably they are monocyclic or bicyclic.
 25 The number of ring members preferably is 5, 6, 8, 9 or 10. The individual rings preferably are 5-membered rings, 6-membered rings or 7-membered rings. Examples of monocyclic and bicyclic heterocyclic systems from which residues occurring in the compounds of the formula I can be derived, are pyrrole, furan, thiophene, imidazole, pyrazole, 1,2,3-triazole, 1,2,4-triazole, 1,3-dioxole, 1,3-oxazole (= oxazole), 1,2-
 30 oxazole (= isoxazole), 1,3-thiazole (= thiazole), 1,2-thiazole (= isothiazole), tetrazole, pyridine, pyridazine, pyrimidine, pyrazine, pyran, thiopyran, 1,4-dioxine, 1,2-oxazine, 1,3-oxazine, 1,4-oxazine, 1,2-thiazine, 1,3-thiazine, 1,4-thiazine, 1,2,3-triazine, 1,2,4-

triazine, 1,3,5-triazine, 1,2,4,5-tetrazine, azepine, 1,2-diazepine, 1,3-diazepine, 1,4-diazepine, 1,3-oxazepine, 1,3-thiazepine, indole, benzothiophene, benzofuran, benzothiazole, benzoxazole, benzimidazole, benzodioxole, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, thienothiophenes, 1,8-naphthyridine and other naphthyridines, pteridin, or phenothiazine, each of them in saturated form (perhydro form) or in partially unsaturated form (for example in the dihydro form or the tetrahydro form) or in maximally unsaturated form or aromatic form, provided that the respective forms are known and stable. The term "aryl" and the term "heteroaryl" as used herein comprise bicyclic residues in which both cycles are aromatic as well as bicyclic residues in which only one cycle is aromatic. The same applies to the term "group Ar" or the term "group Hetar". Suitable heterocycles include, for example, the saturated heterocycles pyrrolidine, piperidine, piperazine, morpholine and thiomorpholine. The degree of saturation of heterocyclic groups is indicated in their individual definitions. Unsaturated heterocycles can contain, for example, 1, 2 or 3, double bonds within the ring system. 5-membered rings and 6-membered rings can in particular also be aromatic.

Residues derived from the mentioned heterocycles can be attached via any suitable carbon atom. Residues derived from nitrogen heterocycles which can carry a hydrogen atom or a substituent on a ring nitrogen atom, such as pyrrole, imidazole, pyrrolidine, morpholine or piperazine residues, can also be attached via a ring nitrogen atom, in particular if the respective heterocyclic residue is attached to a carbon atom. For example, a thienyl residue can be present as 2-thienyl residue or 3-thienyl residue, a furyl residue as 2-furyl residue or 3-furyl residue, a pyridyl residue as 2-pyridyl residue, 3-pyridyl residue or 4-pyridyl residue, a piperidinyl residue as 1-piperidinyl residue (= piperidino residue), 2-piperidinyl residue, 3-piperidinyl residue or 4-piperidinyl residue, a (thio)morpholinyl residue as 2-(thio)morpholinyl residue, 3-(thio)morpholinyl residue or 4-(thio)morpholinyl residue (= thiomorpholino residue). A residue derived from 1,3-thiazole or imidazole which is attached via a carbon atom can be attached via the 2-position, the 4-position or the 5-position.

In case a heterocyclic groups is substituted, it can carry one or more, for example 1, 2, 3 or 4, identical or different substituents. Substituents in heterocycles can be present in any desired positions, for example in a 2-thienyl residue or 2-furyl residue in the 3-position and/or in the 4-position and/or in the 5-position, in a 3-thienyl residue or 3-furyl residue in the 2-position and/or in the 4-position and/or in the 5-position, in a 2-pyridyl residue in the 3-position and/or in the 4-position and/or in the 5-position and/or in the 6-position, in a 3-pyridyl residue in the 2-position and/or in the 4-position and/or in the 5-position and/or in the 6-position, in a 4-pyridyl residue in the 2-position and/or in the 3-position and/or in the 5-position and/or in the 6-position. Suitable nitrogen heterocycles can also be present as N-oxides or as quaternary salts containing a counterion which is derived from a pharmaceutically acceptable acid. Pyridine moieties, for example, can thus be present as pyridine-N-oxides.

Halogen is fluorine, chlorine, bromine oder iodine, preferably fluorine or chlorine.

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The present invention includes all stereoisomeric forms of the compounds of the formula I. Centers of asymmetry that are present in the compounds of formula I all independently from one another can have S configuration or R configuration. The invention includes all possible enantiomers and diastereomers and mixtures of two or more stereoisomers, for example mixtures of enantiomers and/or diastereomers, in all ratios. Thus, compounds of the present invention which can exist as enantiomers can be present in enantiomerically pure form, both as levorotatory and as dextrorotatory antipodes, in the form of racemates and in the form of mixtures of the two enantiomers in all ratios. In the case of a cis/trans isomerism the invention includes both the cis form and the trans form as well as mixtures of these forms in all ratios. All these forms are a subject of the present invention. The preparation of individual stereoisomers can be carried out, if desired, by separation of a mixture by customary methods, for example by chromatography or crystallization, by the use of stereochemically uniform starting materials for the synthesis or by stereoselective synthesis. Optionally a derivatization can be carried out before a separation of stereoisomers. The separation of a mixture of stereoisomers can be carried out at the stage of the compounds of the formula I or at the stage of an intermediate during the

synthesis or at the stage of a starting compound. The present invention also includes all tautomeric forms of the compounds of formula I.

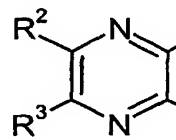
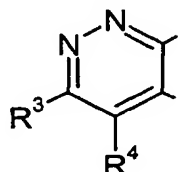
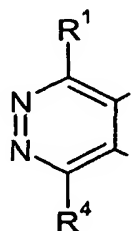
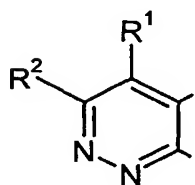
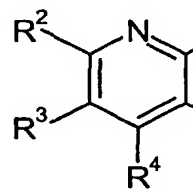
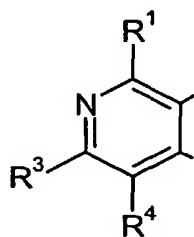
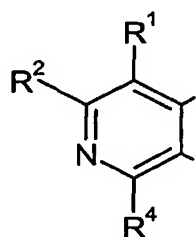
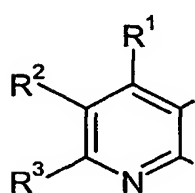
In case the compounds of formula I contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the formula I which contain acidic groups can be present on these groups and can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. Examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula I which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples of suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfamic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the formula I simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The salts of the compounds of the formula I can be obtained by customary methods which are known to the person skilled in the art like, for example, by contacting the compound of the formula I with an organic or inorganic acid or base in a solvent or diluent, or by anion exchange or cation exchange from another salts. The present invention also includes all salts of the compounds of the formula I which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

The present invention furthermore includes all solvates of compounds of the formula I, for example hydrates and adducts with alcohols, active metabolites of the compounds of the formula I, and also derivatives and prodrugs of the compounds of the formula I which contain physiologically tolerable and cleavable groups, for example esters, amides and compounds in which the N-H group depicted in formula I is replaced with an N-alkyl group, such as N-methyl, or with an N-acyl group, such as N-acetyl or N-argininyl, including pharmaceutically acceptable salts formed on functional groups present in the N-acyl group.

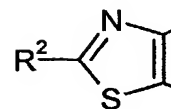
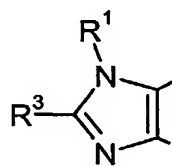
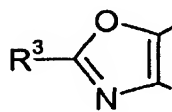
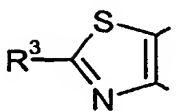
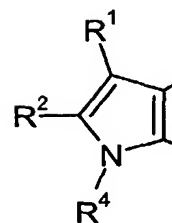
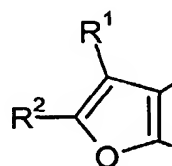
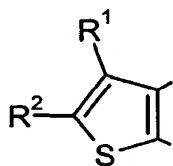
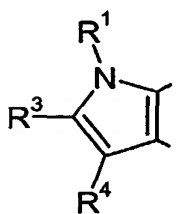
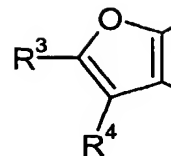
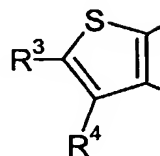
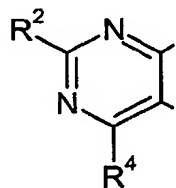
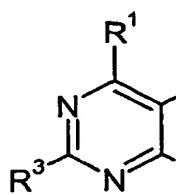
- 10 In preferred embodiments of the present invention, one or more of the structural moieties in the compounds of formula I, including the number n, the ring A, the substituents R¹ to R⁵ and the other groups present in the compounds of formula I, independently from each other have the following preferred meanings, more preferred meanings, even more preferred meanings or most preferred meanings.

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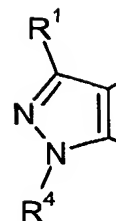
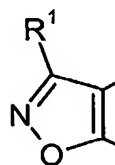
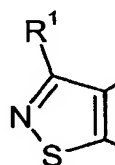
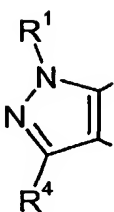
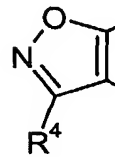
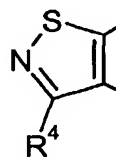
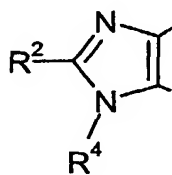
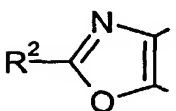
In a preferred embodiment of the present invention the 5-membered or 6-membered monocyclic ring A which has two carbon atoms in common with the cycloalkenyl ring in formula I, is preferably selected from the following rings:



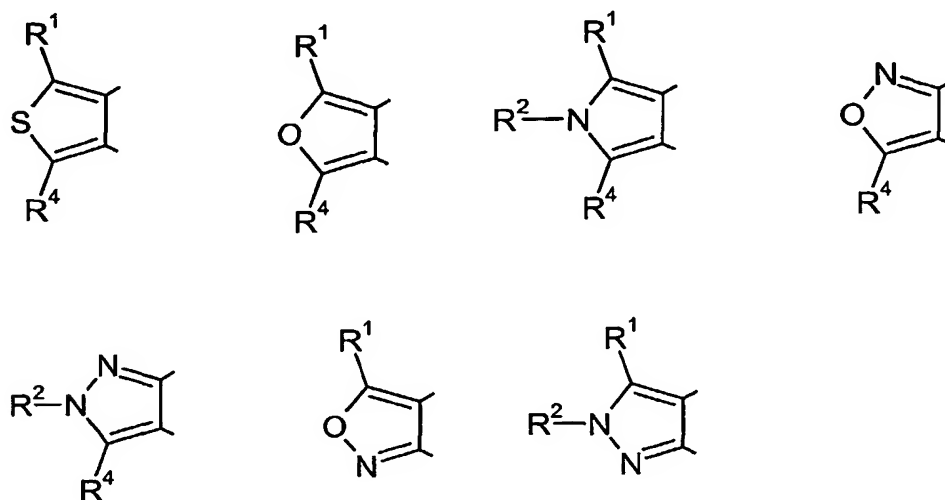
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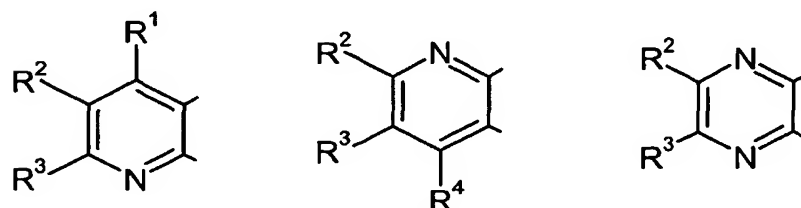


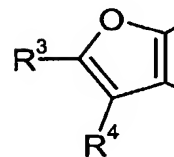
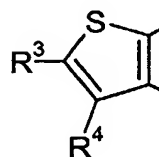
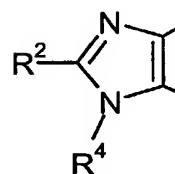
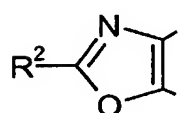
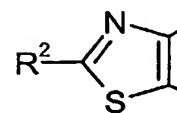
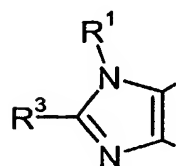
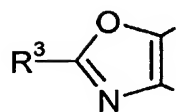
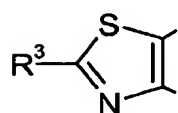
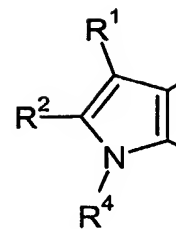
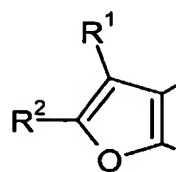
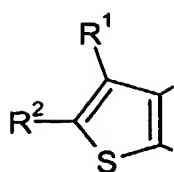
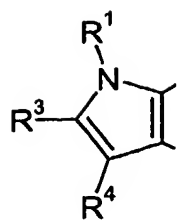
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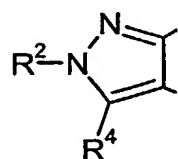
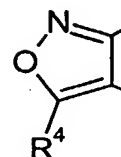
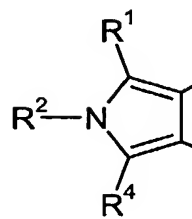
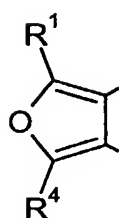
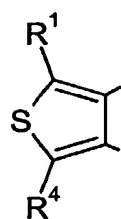
- 5 In the formulae of the specific rings A above and below the upper of the two free bonds is directed towards the CH_2 group in the condensed cycloalkenyl ring in formula I and the lower of the two free bonds is directed to the $(\text{CH}_2)_n$ group in formula I.
- 10 In another preferred embodiment of the present invention the ring A is an aromatic 6-membered ring containing 1 or 2 nitrogen atoms, in particular 1 nitrogen atom, as ring heteroatoms. In a further preferred embodiment of the present invention the ring A is an aromatic 5-membered ring containing a sulfur atom as ring heteroatom or a sulfur atom and a nitrogen atom as ring heteroatoms, in particular a ring containing
- 15 a sulfur atom as ring heteroatom.

More preferably A is selected from the following rings:



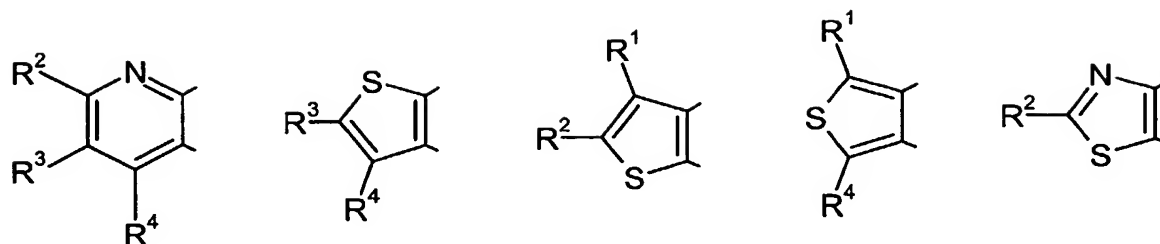


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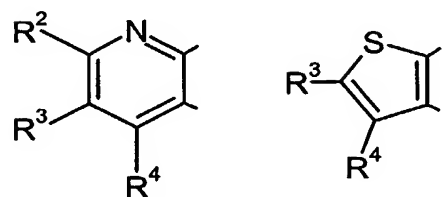


10

Even more preferably the ring A is selected from the following rings:



Most preferably the ring A is selected from the following rings:

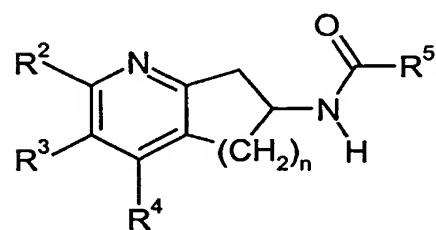


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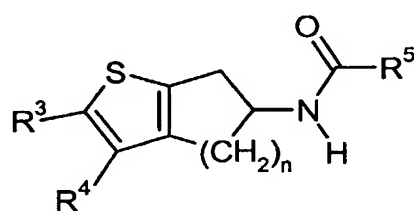
Thus, if one of the two most preferred rings A is present in the compounds of the formula I, the compounds of the formula I are the compounds of the formulae Ia or Ib, more specifically the 6,7-dihydro-5H-cyclopenta[b]pyridines of the formula Ic (also called pyridines), the 5,6,7,8-tetrahydroquinolines of the formula Id (which may also be designated as 5,6,7,8-tetrahydrobenzo[b]pyridines), the 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridines of the formula Ie, the 5,6-dihydro-4H-cyclopenta[b]thiophenes of the formula If, the 4,5,6,7-tetrahydrobenzo[b]thiophenes of the formula Ig, or the 5,6,7,8-tetrahydro-4H-cyclohepta[b]thiophenes of the formula Ih, respectively. In the compounds of the formulae Ia to Ih the number n and the residues R² to R⁵ can have any of the general or preferred or specific meanings indicated above or below.

10

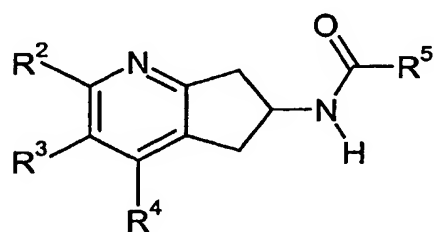
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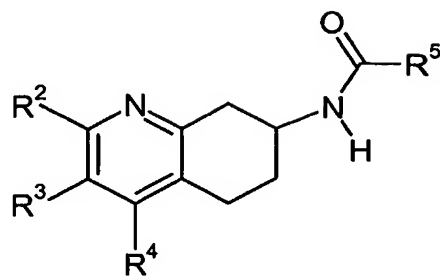
Ia



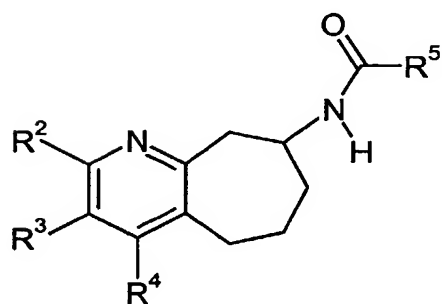
Ib



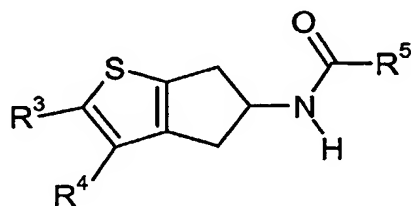
Ic



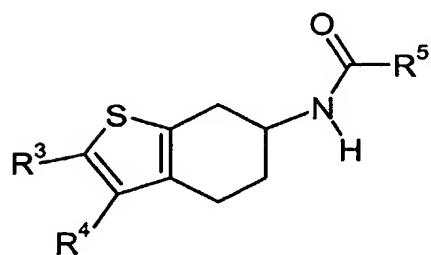
Id



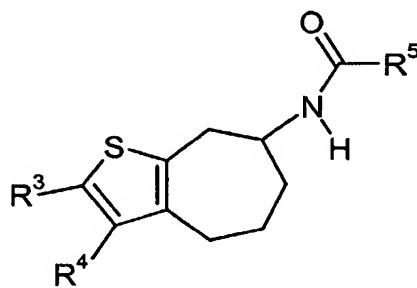
Ie



If



Ig



Ih

5

R¹ is preferably selected from the group consisting of: H; C₁-C₄-alkyl; C₁-C₄-alkoxy; CF₃; halogens; -CN; C₁-C₄-alkyl-S(O)_m; and unsubstituted and at least monosubstituted phenyl and heteroaryl the substituents of which are selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃, where heteroaryl is selected from the group consisting of 5-membered and 6-membered heterocycles containing one or more heteroatoms selected from the group consisting of N, O, and S. More preferably R¹ is H, halogen or C₁-C₄-alkyl.

10

R^2 is preferably selected from the group consisting of H, halogens, -CN and C_1 - C_4 -alkyl, more preferably from the group consisting of H, halogens and C_1 - C_4 -alkyl. Even more preferably R^2 is H.

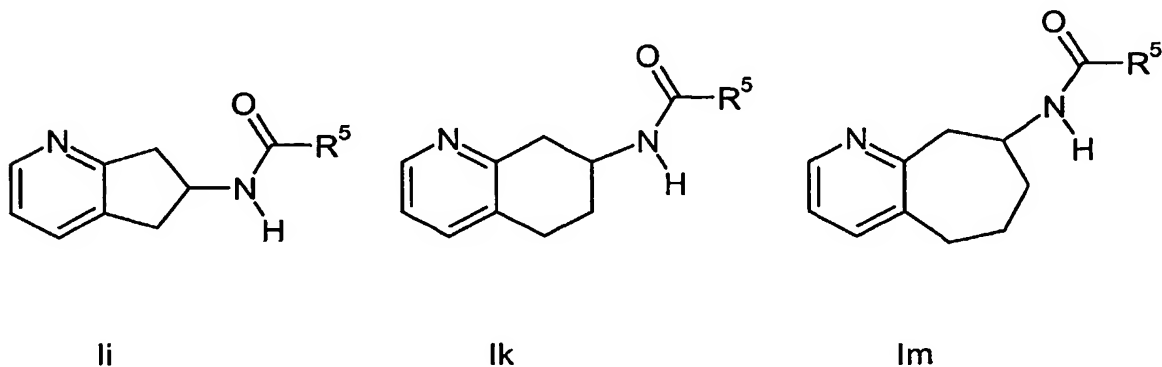
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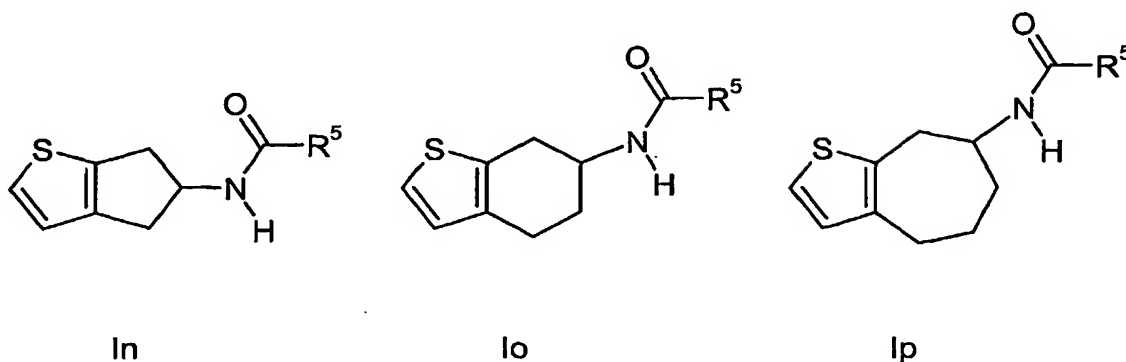
R^3 is preferably selected from the group consisting of H, halogens, -CN, and C_1 - C_4 -alkyl, more preferably from the group consisting of H, halogens, and C_1 - C_4 -alkyl. Even more preferably R^3 is H.

- 10 R^4 is preferably selected from the group consisting of: H; C_1 - C_4 -alkyl; C_1 - C_4 -alkoxy; CF_3 ; halogens; -CN; C_1 - C_4 -alkyl- $S(O)_m$; and unsubstituted and at least monosubstituted phenyl and heteroaryl the substituents of which are selected from the group consisting of halogens, -CN, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy and CF_3 , where heteroaryl is selected from the group consisting of 5-membered and 6-membered
- 15 heterocycles containing one or more heteroatoms selected from the group consisting of N, O, and S. More preferably R^4 is H, halogen or C_1 - C_4 -alkyl.

In particular each of R^1 , R^2 , R^3 and R^4 is H. As example of compounds in which R^1 , R^2 , R^3 and R^4 are H, the following compounds of the formulae li, lk, lm, ln, lo and lp may be mentioned in which R^5 can have any of the general or preferred or specific meanings indicated above or below.

20





R^5 is preferably a group Ar or a group Hetar both of which are unsubstituted or carry one or more identical or different substituents selected from the group consisting of:

5 halogens; -CN; NH_2 ; unsubstituted and at least monosubstituted C_1 - C_8 -alkyl, C_2 - C_8 -alkenyl, C_2 - C_8 -alkynyl, C_1 - C_8 -alkoxy, C_1 - C_8 -alkylamino and di(C_1 - C_8 -alkyl)amino, the substituents of which are selected from the group consisting of F, OH, C_1 - C_6 -alkoxy, phenoxy, C_1 - C_6 -alkylmercapto, NH_2 , C_1 - C_6 -alkylamino and di(C_1 - C_6 -alkyl)amino; C_3 - C_5 -alkandiyl; phenyl; heteroaryl; phenyl-substituted or heteroaryl-substituted C_1 - C_2 -

10 alkyl; CF_3 ; OH; phenoxy; benzyloxy; (C_1 - C_6 -alkyl)-COO; $S(O)_m$ -(C_1 - C_6 -alkyl) which can optionally be substituted by OH or C_1 - C_6 -alkoxy; $S(O)_m$ -phenyl; $S(O)_m$ -heteroaryl; SH; phenylamino; benzylamino; (C_1 - C_6 -alkyl)-CONH-; (C_1 - C_6 -alkyl)-CON(C_1 - C_4 -alkyl)-; phenyl-CONH-; phenyl-CON(C_1 - C_4 -alkyl)-; heteroaryl-CONH-; heteroaryl-CON(C_1 - C_4 -alkyl)-; (C_1 - C_6 -alkyl)-CO-; phenyl-CO-; heteroaryl-CO-; CF_3 -CO-;

15 -OCH₂O-; -OCF₂O-; -OCH₂CH₂O-; -CH₂CH₂O-; COO(C_1 - C_6 -alkyl); -CONH₂; -CONH(C_1 - C_6 -alkyl); -CON(di(C_1 - C_6 -alkyl)); C(NH)-NH₂; -SO₂NH₂; -SO₂NH(C_1 - C_6 -alkyl); -SO₂NH(phenyl); -SO₂N(di(C_1 - C_6 -alkyl)); C_1 - C_6 -alkyl-SO₂NH-; (C_1 - C_6 -alkyl)-SO₂N(C_1 - C_6 -alkyl)-; phenyl-SO₂NH-; phenyl-SO₂N(C_1 - C_6 -alkyl)-; heteroaryl-SO₂NH-; heteroaryl-SO₂N(C_1 - C_6 -alkyl)-; and a residue of a saturated or at least

20 monounsaturated aliphatic, mononuclear 5-membered to 7-membered heterocycle containing 1, 2 or 3 heteroatoms selected from the group consisting of N, O and S, which heterocycle can be substituted by one or more substituents selected from the group consisting of halogens, C_1 - C_3 -alkyl, C_1 - C_3 -alkoxy, OH, oxo and CF_3 , where said heterocycle can optionally be condensed to the said group Ar or the said group

25 Hetar; wherein all heteroaryl, phenyl, heteroaryl-containing and phenyl-containing

groups, which are optionally present in the said substituents of the said group Ar or the said group Hetar, can be substituted by one or more substituents selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, OH, C₁-C₃-alkoxy, and CF₃.

- 5 R⁵ is more preferably phenyl or a group Hetar both of which are unsubstituted or carry one or more identical or different substituents selected from the group consisting of: halogens; -CN; NH₂; unsubstituted and at least monosubstituted C₁-C₆-alkyl, C₂-C₆-alkenyl, C₂-C₆-alkynyl, C₁-C₃-alkoxy, C₁-C₄-alkylamino and di(C₁-C₄-alkyl)amino, the substituents of which are selected from the group consisting of F, C₁-C₃-alkoxy, C₁-C₃-alkylmercapto and NH₂; C₃-C₅-alkandiyl; phenyl; heteroaryl; phenyl-substituted or heteroaryl-substituted C₁-C₂-alkyl; CF₃; OH; (C₁-C₄-alkyl)-COO; S(O)_m-(C₁-C₄-alkyl); (C₁-C₄-alkyl)-CONH-; (C₁-C₄-alkyl)-CON(C₁-C₄-alkyl)-; (C₁-C₄-alkyl)-CO-; phenyl-CO-; heteroaryl-CO-; CF₃-CO-; -OCH₂O-; -OCF₂O-; -OCH₂CH₂O-; -CH₂CH₂O-; COO(C₁-C₆-alkyl); -CONH₂; -CONH(C₁-C₄-alkyl); -CON(di(C₁-C₄-alkyl)); C(NH)-NH₂; -SO₂NH₂; -SO₂NH(C₁-C₄-alkyl); -SO₂NH(phenyl); -SO₂N(di(C₁-C₄-alkyl)); (C₁-C₄-alkyl)-SO₂NH-; (C₁-C₄-alkyl)-SO₂N(C₁-C₄-alkyl)-; and a residue of a saturated or at least monounsaturated aliphatic, mononuclear 5-membered to 7-membered heterocycle containing 1, 2 or 3 heteroatoms selected from the group consisting of N, O and S, which heterocycle can be substituted by one or more substituents selected from the group consisting of halogens, C₁-C₃-alkyl, C₁-C₃-alkoxy, OH, oxo and CF₃, where said heterocycle can optionally be condensed to the said phenyl or the said group Hetar; wherein all heteroaryl, phenyl, heteroaryl-containing and phenyl-containing groups, which are optionally present in the said substituents of the said phenyl or the said group Hetar, can be substituted by one or more substituents selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, OH, C₁-C₃-alkoxy, and CF₃.

- R⁵ is even more preferably phenyl or a group Hetar both of which are unsubstituted or carry one or more identical or different substituents selected from the group consisting of: F; Cl; Br; C₁-C₃-alkyl; C₁-C₃-alkoxymethyl; 2-amino-3,3,3-trifluoropropyl-; CF₃; C₃-C₅-alkandiyl; phenyl; heteroaryl; benzyl; heteroaryl-methyl-; OH; C₁-C₃-alkoxy; phenoxy; trifluoromethoxy; 2,2,2-trifluoroethoxy; (C₁-C₄-alkyl)-

COO; C₁-C₃-alkylmercapto; phenylmercapto; C₁-C₃-alkylsulfonyl; phenylsulfonyl; NH₂; C₁-C₄-alkylamino; di(C₁-C₄-alkyl)amino; (C₁-C₃-alkyl)-CONH-; (C₁-C₃-alkyl)-SO₂NH-; (C₁-C₃-alkyl)-CO-; phenyl-CO-; -OCH₂O-; -OCF₂O-; -CH₂CH₂O-; COO(C₁-C₄-alkyl); -CONH₂; -CONH(C₁-C₄-alkyl); -CON(di(C₁-C₄-alkyl)); -CN; -SO₂NH₂; 5 -SO₂NH(C₁-C₄-alkyl); -SO₂N(di(C₁-C₄-alkyl)); pyrrolidinyl; piperidinyl; morpholinyl and thiomorpholinyl; wherein all heteroaryl, phenyl, heteroaryl-containing and phenyl-containing groups, which are optionally present in the said substituents of the said phenyl or the said group Hetar, can be substituted by one or more substituents selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, OH, C₁-C₃-alkoxy, 10 and CF₃.

R⁵ is most preferably selected from the group consisting of 4-fluorophenyl, 4-chlorophenyl, 4-bromophenyl, 4-(C₁-C₃-alkoxy)-phenyl, 4-trifluoromethoxyphenyl, 2-bromo-4-fluorophenyl, 2-chloro-4-fluorophenyl, 3,4-dimethylphenyl, 2,4- 15 dimethylphenyl, 4-chloro-2-methylphenyl, 2-hydroxy-4-methylphenyl, 2-hydroxy-4-ethoxyphenyl, 2-methoxy-4-methylphenyl, 4-phenoxyphenyl, 3-fluoro-4-methylphenyl, benzo[1,3]dioxol-5-yl, 2,2-difluoro-benzo[1,3]dioxol-5-yl, 2,3-dihydrobenzofuran-5-yl, 1-(4-chlorophenyl)-5-trifluoromethyl-1H-pyrazole-4-yl, 1-(4-fluorophenyl)-3,5-dimethyl-1H-pyrazole-4-yl, 1H-benzotriazole-5-yl, 1H-indole-4-yl, 1H-indole-6-yl, 1- 20 isopropyl-2-trifluoromethyl-1H-benzimidazole-5-yl, 1-methyl-3-oxo-1,2,3,4-tetrahydroquinoxaline-6-yl, 1-phenyl-5-trifluoromethyl-1H-pyrazole-4-yl, 2-(2-hydroxypyridin-4-yl)-1H-benzimidazole-5-yl, 2-(4-cyanophenyl)-1H-benzimidazole-5-yl, 2,4-dimethyloxazole-5-yl, 2,4-dimethylpyrimidine-5-yl, 2,4-dimethylthiazole-5-yl, 2,5-dimethyl-1H-pyrrole-3-yl, 2,5-dimethyl-1-phenyl-1H-pyrrole-3-yl, 2,5-dimethyl-1- 25 (pyridin-4-ylmethyl)-1H-pyrrole-3-yl, 2,5-dimethyl-2H-pyrazole-3-yl, 2,6-dichloropyridin-3-yl, 2,6-dimethoxypyridin-3-yl, 2,6-dimethylpyridin-3-yl, 2-amino-4,6-dimethylpyridin-3-yl, 2-amino-6-chloropyridin-3-yl, 2-aminopyridin-3-yl, 2-chloro-6-methylpyridin-3-yl, 2-chloropyridin-4-yl, 2-cyclopropyl-4-methylthiazole-5-yl, 2-dimethylamino-4-methylthiazole-5-yl, 2-dimethylaminopyridin-4-yl, 2-ethyl-5-methyl-2H-pyrazole-3-yl, 2- 30 hydroxy-6-methylpyridin-3-yl, 2-methyl-1H-benzimidazole-5-yl, 2-methyl-3H-benzimidazole-5-yl, 2-methylpyridin-3-yl, 2-methyl-6-trifluoromethylpyridin-3-yl, 2-methylthiazole-5-yl, 2-(morpholin-4-yl)-pyridin-4-yl, 2-(morpholin-4-yl)-pyrimidine-5-yl,

- 2-(pyrrolidin-1-yl)-pyridin-4-yl, 3,5-dimethyl-1H-pyrazole-4-yl, 3-amino-5,6-dimethylpyrazine-2-yl, 3-amino-5-methylpyrazine-2-yl, 3-aminopyrazine-2-yl, 3-dimethylamino-4-methylphenyl, 3-dimethylaminophenyl, 3H-benzimidazole-5-yl, 1H-benzimidazole-5-yl, 3-methylsulfonylamino-2-methylphenyl, 3-
- 5 methylsulfonylaminophenyl, 3-methylisoxazole-4-yl, 3-(morpholin-4-yl)-phenyl, 3-(piperidin-1-yl)-phenyl, 3-(pyrrolidin-1-yl)-phenyl, 4-(2,2,2-trifluoroethoxy)phenyl, 4,6-dimethylpyrid-3-yl, 4-amino-2-ethylsulfanylpurimidine-5-yl, 4-amino-2-methylpyrimidine-5-yl, 4-chloro-3-methylsulfonylaminophenyl, 4-chloro-3-sulfamoylphenyl, 4-methyl-3-methylaminophenyl, 4-methylthiazole-5-yl, pyridine-2-yl,
- 10 5,6,7,8-tetrahydroquinoline-3-yl, 5-amino-1-phenyl-1H-pyrazole-4-yl, 5-methylsulfonyl-2-methylphenyl, 5-methyl-1-phenyl-1H-pyrazole-4-yl, 5-methylisoxazole-3-yl, 5-methylpyrid-3-yl, 5-methylpyrazine-2-yl, 6-chloropyrid-3-yl, 6-cyanopyrid-3-yl, 6-dimethylaminopyrid-3-yl, 6-ethynylpyrid-3-yl, 6-methoxymethylpyrid-3-yl, 6-methoxypyrid-3-yl, 6-methyl-2-methylaminopyrid-3-yl, 6-
- 15 methylaminopyrazine-2-yl, 6-methylpyrid-3-yl, 6-(morpholin-4-yl)-pyrid-3-yl, 6-(pyrrolidin-1-yl)-pyrid-3-yl, imidazo[1,2-a]pyridine-2-yl, 6-trifluoromethylpyrid-3-yl, pyrimidine-4-yl, 4-methylsulfanylphenyl, 4-ethylsulfanylphenyl, 3-methoxycarbonylphenyl, 4-methoxycarbonylphenyl, 3-ethoxycarbonylphenyl, 4-ethoxycarbonylphenyl, 2-bromo-4-chlorophenyl, 2,3-dichlorophenyl, 3-chloro-4-
- 20 (isopropylsulfonyl)thiophene-2-yl, 4-bromo-2-chlorophenyl, 4-methoxyphenyl, 4-ethoxyphenyl, 3-methoxyphenyl, 3-ethoxyphenyl, 2-methyl-thiophene-3-yl, 3-chloro-4-methyl-thiophene-2-yl, 5-bromo-thiophene-2-yl, 5-chloro-thiophene-2-yl, 5-methyl-thiophene-2-yl, 4-methyl-thiophene-2-yl, 3-methyl-thiophene-2-yl, 5-acetyl-thiophene-2-yl, pyridine-3-yl, pyridine-4-yl, 4-trifluoromethylphenyl, 4-ethylaminophenyl, 4-
- 25 methylaminophenyl, 2-aminophenyl, 4-bromo-2-fluorophenyl, 2-chlorophenyl, 3-chloro-4-methylphenyl, 4-chloro-3-methylphenyl, 2-chloro-3-methylphenyl, 2-methylphenyl, 2-acetoxy-4-methylphenyl, 2-acetoxy-4-ethoxyphenyl, 2-acetoxy-4-methoxyphenyl, 4-trifluoromethylsulfanylphenyl, naphthalene-2-yl, 1,1-dimethylindan-4-yl, 3-isobutylaminophenyl, 3-(2,2-dimethylpropionylamino)phenyl, 2-bromophenyl,
- 30 2-fluorophenyl, 3-bromo-5-methylthiophene-2-yl, 3-chloro-6-fluorobenzo[b]thiophene-2-yl and 3,4-dichlorobenzo[b]thiophene-2-yl.

Heteroaryl is preferably a residue of a 5-membered to 10-membered, aromatic, monocyclic or bicyclic heterocycle containing 1, 2 or 3 heteroatoms selected from the group consisting of N, O and S. More preferably heteroaryl is selected from the group consisting of furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridazinyl, pyrazinyl, pyridyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolyl, indolyl, benzofuranyl, benzodioxolyl, benzothiophenyl and indazolyl.

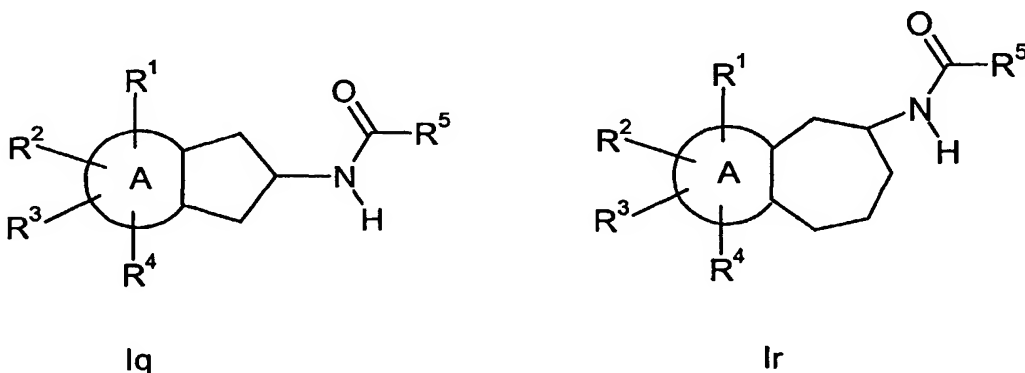
The group Hetar is preferably a residue of a 5-membered to 10-membered, aromatic, mono- or bicyclic heterocycle containing 1, 2 or 3 heteroatoms selected from the group consisting of N, O and S. More preferably the group Hetar is selected from the group consisting of furyl, pyrrolyl, thienyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, pyridazinyl, pyrazinyl, pyridyl, pyrimidinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinoxalinyl, quinazolyl, indolyl, benzofuranyl, benzodioxolyl, benzothiophenyl and indazolyl.

Aryl is preferably phenyl.

m is preferably 0 or 2.

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n is preferably 1 or 3. I.e., in a preferred embodiment of the invention the compounds of formula I are acylated heteroaryl-condensed cyclopentenylamines of the formula Iq (also designated as cyclopenta-condensed heteroarene derivatives), or acylated cycloheptenylamines of the formula Ir (also designated as cyclohepta-condensed heteroarenes). In the compounds of the formulae Iq and Ir the ring A and the residues R¹ to R⁵ can have any of the general or preferred or specific meanings indicated above or below.



Preferred compounds of the formula I are those compounds in which one or some or all of the structural moieties and groups contained therein have preferred meanings, more preferred meanings, even more preferred meanings or most preferred meanings defined above, all combinations of such preferred meanings etc. and/or of specific meanings of a group being a subject of the present invention. With respect to all preferred compounds of the formula I the present invention also includes all stereoisomeric forms and mixtures thereof in all ratios, and their pharmaceutically acceptable salts.

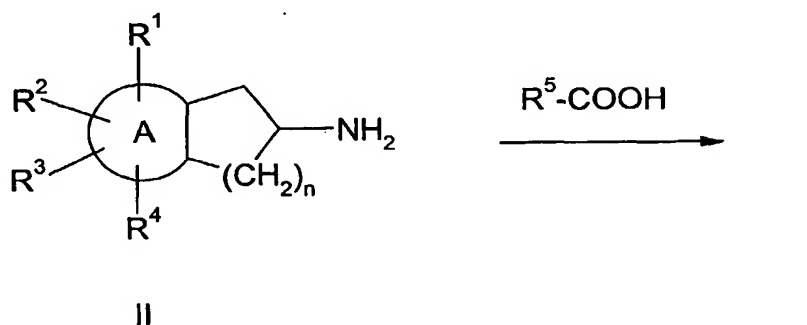
As examples of specific compounds, which are a subject of the present invention in all their stereoisomeric forms and in the form of mixtures thereof in all ratios, and in the form of their pharmaceutically acceptable salts, the following compounds may be mentioned:

- 4-fluoro-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)benzamide,
- 4-chloro-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)benzamide,
- 2,4-dimethyl-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)benzamide,
- 2,4-dichloro-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)benzamide,
- 2,2-difluorobenzo[1,3]dioxole-5-carboxylic acid (6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)amide,
- 2,6-dimethyl-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)nicotinamide,
- 6-methoxymethyl-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)nicotinamide,
- 6-methoxy-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)nicotinamide,

- 2,5-dimethyl-1-phenyl-1H-pyrrole-3-carboxylic acid (6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)amide,
 2-methyl-1H-benzimidazole-5-carboxylic acid (6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)amide,
- 5 2,5-dimethyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)amide,
 2,4-dichloro-N-(6,7-dihydro-5H-[1]pyrindin-6-yl)benzamide,
 2,5-dimethyl-1-phenyl-1H-pyrrole-3-carboxylic acid (6,7-dihydro-5H-[1]pyrindin-6-yl)amide,
- 10 2,5-dimethyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (6,7-dihydro-5H-[1]pyrindin-6-yl)amide,
 N-(5,6-dihydro-4H-cyclopenta[b]thiophen-5-yl)-4-fluorobenzamide,
 4-chloro-N-(5,6-dihydro-4H-cyclopenta[b]thiophen-5-yl)benzamide,
 N-(5,6-dihydro-4H-cyclopenta[b]thiophen-5-yl)-2,4-dimethylbenzamide,
- 15 2,4-dichloro-N-(5,6-dihydro-4H-cyclopenta[b]thiophen-5-yl)benzamide,
 2,2-difluorobenzo[1,3]dioxole-5-carboxylic acid (5,6-dihydro-4H-cyclopenta[b]thiophen-5-yl)amide,
 N-(5,6-dihydro-4H-cyclopenta[b]thiophen-5-yl)-2,6-dimethylnicotinamide,
 N-(5,6-dihydro-4H-cyclopenta[b]thiophen-5-yl)-6-methoxymethylnicotinamide,
- 20 N-(5,6-dihydro-4H-cyclopenta[b]thiophen-5-yl)-6-methoxynicotinamide,
 2,5-dimethyl-1-phenyl-1H-pyrrole-3-carboxylic acid (5,6-dihydro-4H-cyclopenta[b]thiophen-5-yl)amide,
 2-methyl-1H-benzimidazole-5-carboxylic acid (5,6-dihydro-4H-cyclopenta[b]thiophen-5-yl)amide,
- 25 2,5-dimethyl-1-(pyridin-4-ylmethyl)-1H-pyrrole-3-carboxylic acid (5,6-dihydro-4H-cyclopenta[b]thiophen-5-yl)amide.

A compound of the formula I or a salt thereof can be prepared, for example, by a process which comprises the acylation of a heteroaryl-condensed cycloalkenylamine

30 of the formula II with a carboxylic acid of the formula $R^5\text{-COOH}$ or a derivative thereof, which process also is a subject of the present invention.



Suitable derivatives of the carboxylic acids of the formula $R^5\text{-COOH}$ are, for example, carboxylic acid chlorides, esters including $C_1\text{-C}_4$ -alkyl esters, such as methyl esters or ethyl esters, optionally substituted aryl esters, such as phenyl esters or nitrophenyl esters, or activated esters, or anhydrides or mixed anhydrides. In the compounds of the formula II and the carboxylic acids of the formula $R^5\text{-COOH}$ and their derivatives the ring A and the groups R^1 , R^2 , R^3 , R^4 and R^5 have the meanings indicated above with respect to the compounds of the formula I, or else functional groups can be present in protected form or in the form of a precursor. For example, when a compound of the formula I is to be prepared which contains a carboxylic acid group or an amino group, it may be appropriate that in the acylation reaction these groups are present in protected form, for example as an ester such as a tert-butyl ester or benzyl ester instead of the free carboxylic acid group, or as an acylated amino group such as a tert-butoxycarbonylamino group or benzyloxycarbonylamino group instead of the free amino group, and only subsequent to the acylation the desired final groups are liberated by deprotection. Suitable protective group strategies which may be used in the synthesis of the compounds of formula I are known to the person skilled in the art. An example of a precursor group of a functional group is the nitro group which can be converted into an amino group by reduction, for example by catalytic hydrogenation, after the acylation reaction.

The acylation reactions can be carried out under standard conditions known to the person skilled in the art. In many cases the reaction is favorably performed in an inert solvent or diluent, for example a hydrocarbon or a chlorinated hydrocarbon, such as toluene, 1,2-dichloroethane or methylene chloride, an ether, such as tetrahydrofuran,

dioxane or 1,2-dimethoxyethane, an alcohol such as methanol, ethanol or isopropanol, an amide such as N,N-dimethylformamide or N-methylpyrrolidone, acetonitrile, water, or a else a mixture of two or more solvents or diluents. Depending on the individual case, it may be advantageous to perform the reaction in the presence of a base, for example an inorganic base such as sodium hydroxide, sodium carbonate or sodium hydrogencarbonate, or an organic base such as triethylamine, ethyldiisopropylamine, N-ethylmorpholine or pyridine, and/or in the presence of an acylation catalyst such as 4-dimethylaminopyridine.

- 10 If a carboxylic acid of the formula $R^5\text{-COOH}$ is to be used in the acylation of a compound of the formula II, it is often advantageous to activate the acid or a salt thereof with a condensation agent or coupling agent, for example an agent like those commonly used in peptide chemistry for the formation of amide bonds. Examples of suitable coupling agents are carbodiimides such as dicyclohexylcarbodiimide or diisopropylcarbodiimide, TOTU, i.e. O-((cyano(ethoxycarbonyl)methylene)amino)-N,N,N',N'-tetramethyluronium tetrafluoroborate, HATU, i. e. O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, chloroformic acid esters like ethyl chloroformate or isobutyl chloroformate, tosyl chloride, propylphosphonic acid anhydride or carbonyldiimidazole. Depending on the individual case, the suitable reaction temperature may lie within a wide range. For example, when employing into the acylation reaction a carboxylic acid in the presence of a coupling agent or a carboxylic acid chloride, the reaction can often be carried out at room temperature.

Subsequent to the acylation reaction, besides the above-mentioned deprotection of protected groups or the conversion of a precursor group into the desired final group, optionally further functionalizations or modifications of the obtained compounds can be carried out and suitable functional groups can, for example, be esterified, amidated, transesterified, hydrolyzed, alkylated, sulfonylated, acylated, reduced, oxidized, converted into a salt, or subjected to other reactions.

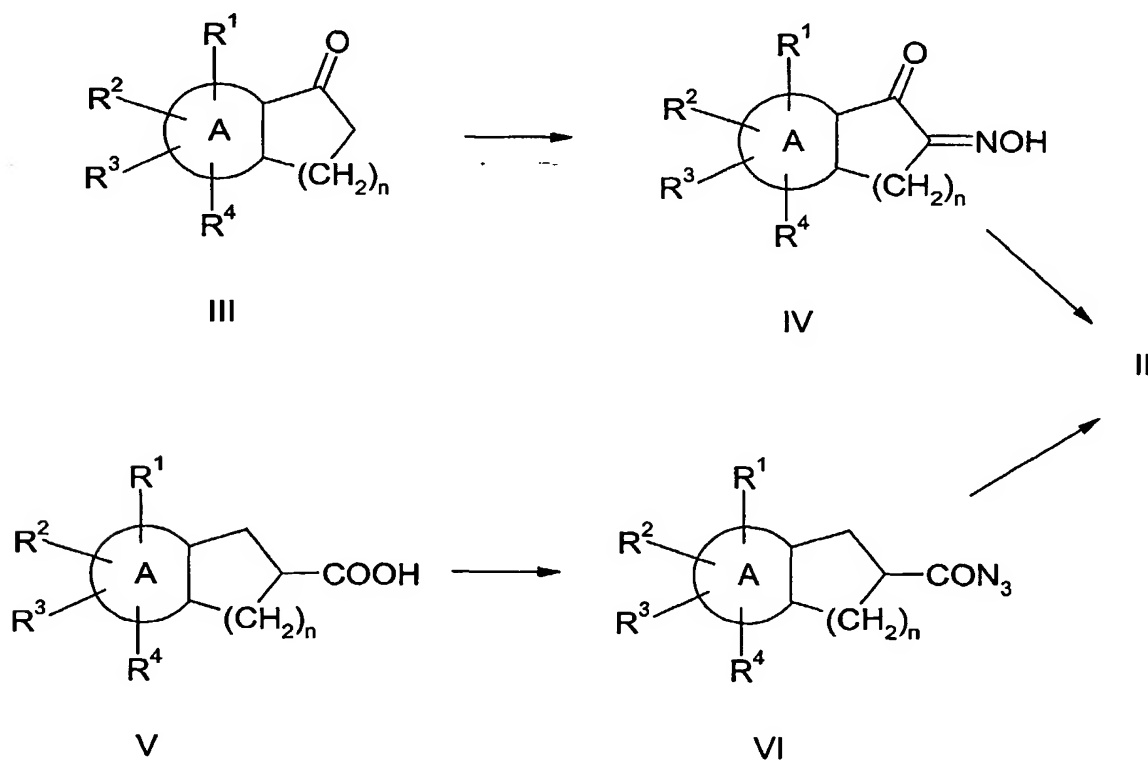
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The starting compounds for the preparation of the compounds of the formula I are commercially available or can be prepared according to or analogously to literature

The starting compounds of the formulae III and V can be obtained as described, for example, in JP 2-255664, EP 853083; WO 98/39300; DE 19942897; CA 2151443; GB 2280438; Schenone et al., *J. Heterocycl. Chem.* 19 (1982) 1355; Bianchi et al., *J. Chem. Res., Synop.*, (1981) 6; Muraro et al., *Bull. Soc. Chim. Fr., Pt. 2*, (1973) 335; 5 Muraro et al., *C. R. Acad. Sci., Ser. C*, 273 (1971) 1362; MacDowell et al., *J. Org. Chem.* 32 (1967) 1226; Ravina et al., *J. Med. Chem.* 43 (2000) 1250; Nayyar et al., *J. Org. Chem.* 62 (1997) 982; Binder et al., *Monatsh. Chem.* 129 (1998) 887; Westerwelle et al., *Chem. Ber.* 124 (1991) 571; Huang et al., *Synth. Commun.* 28 (1998) 1197; Reimann et al., *Pharmazie* 50 (1995) 589; Caprathe et al., *J. Med.* 10 *Chem.* 34 (1991) 2736; Hoffman et al., *J. Org. Chem.* 49 (1984) 193; Schroeder et al., *Eur. J. Med. Chem. - Chim. Ther.* 14 (1979) 309; Ruangsiyanand et al., *Chem. Ber.* 103 (1970) 2403; Dammertz et al., *Arch. Pharm.* 310 (1977) 172; Hicks et al., *J. Chem. Soc., Perkin Trans. 1*, (1984) 2297; Jones et al., *J. Chem. Soc., Perkin Trans. 1*, (1973) 968; EP 745598 or WO 94/04531, or by using methods analogous to those 15 described in these references.

All reactions for the synthesis of the compounds of the formula I are per se well-known to the skilled person and can be carried out under standard conditions according to or analogously to procedures described in the literature, for example in 20 Houben-Weyl, *Methoden der Organischen Chemie* (Methods of Organic Chemistry), Thieme-Verlag, Stuttgart, or *Organic Reactions*, John Wiley & Sons, New York. As mentioned above, depending on the circumstances of the individual case, in order to avoid side reactions during the synthesis of a compound of the formula I, in any reaction step it can be necessary or advantageous to temporarily block functional 25 groups by introducing protective groups and to deprotect them in a later stage of the synthesis, or introduce functional groups in the form of precursor groups which in a later reaction step are converted into the desired functional groups. Such synthesis strategies and protective groups and precursor groups which are suitable in an individual case are known to the skilled person. If desired, the compounds of the 30 formula I can be purified by customary purification procedures, for example by recrystallization or chromatography.

procedures. Routes for the preparation of the compounds of formula II include, for example, the conversion of a ketone of the formula III into an oxime of the formula IV and the conversion of the latter into a compound of the formula II, and the conversion of a carboxylic acid of the formula V into a carboxylic acid azide of the formula VI and the conversion of the latter into a compound of the formula II. The mentioned conversions can be carried out under standard conditions known to the person skilled in the art. For example, a ketone of the formula III can be converted into an oxime of the formula IV by treatment with an organic nitrite such as isoamyl nitrite in the presence of hydrochloric acid, and the reduction of the oxime group to give the amino group and the reduction of the C=O group in benzylic position to give the CH₂ group can be accomplished simultaneously by catalytic hydrogenation in the presence of, for example, palladium. A carboxylic acid of the formula V can be converted into a carboxylic acid azide of the formula VI by reaction with diphenylphosphoryl azide, for example, and the latter be subjected to a Curtius rearrangement.



The compounds of the formula I are useful pharmaceutically active compounds which upregulate the expression of endothelial NO synthase and can be employed as medicaments for the treatment of various diseases. In the context of the present invention, treatment is understood as comprising both therapy, including alleviation and cure, of disease symptoms and prevention or prophylaxis of disease symptoms, such as, for example, the prevention of the appearance of asthmatic disease symptoms or the prevention of myocardial infarction or of myocardial reinfarction in relevant patients. The diseases or disease symptoms can be acute or chronic. Diseases which can be treated with the compounds of the formula I include, for example, cardiovascular diseases like stable and unstable angina pectoris, coronary heart disease, Prinzmetal angina (spasm), acute coronary syndrome, heart failure, myocardial infarction, stroke, thrombosis, peripheral artery occlusive disease (PAOD), endothelial dysfunction, atherosclerosis, restenosis, endothel damage after PTCA, hypertension including essential hypertension, pulmonary hypertension and secondary hypertension (renovascular hypertension, chronic glomerulonephritis), erectile dysfunction and ventricular arrhythmia. Further, the compounds of the formula I lower the cardiovascular risk of postmenopausal women and of women taking contraceptives. Compounds of the formula I can additionally be used in the treatment, i. e. the therapy and prevention, of diabetes and diabetes complications (nephropathy, retinopathy), angiogenesis, asthma bronchiale, chronic renal failure, cirrhosis of the liver, osteoporosis, restricted memory performance or a restricted ability to learn. Preferred indications are stable angina pectoris, coronary heart disease, hypertension, endothelial dysfunction, atherosclerosis and diabetes complications.

The compounds of the formula I can be used in combination with other pharmaceutically active compounds, preferably with compounds which are able to enhance the effect of the compounds of the formula I. Examples of such other compounds include statins; ACE inhibitors; AT1 antagonists; argininase inhibitors; PDE V inhibitors; calcium antagonists; alpha blockers; beta blockers; thiamazole (methimazole) and analogous compounds; arginine; tetrahydrobiopterin; vitamins, in particular vitamin C and vitamin B6; niacine.

The compounds of the formula I and their pharmaceutically acceptable salts, optionally in combination with other pharmaceutically active compounds, can be administered to animals, preferably to mammals, and in particular to humans, as pharmaceuticals by themselves, in mixtures with one another or in the form of pharmaceutical preparations. Further subjects of the present invention therefore also are the compounds of the formula I and their pharmaceutically acceptable salts for use as pharmaceuticals, their use as transcription stimulating agents or upregulating agents of endothelial NO synthase, for example in conditions in which an increased expression of said enzyme or an increased NO level or the normalization of a decreased NO level in a patient is desired, and in particular their use in the treatment, i. e. the therapy and prevention, of the above-mentioned syndromes, as well as their use for preparing medicaments for these purposes. Furthermore, a subject of the present invention are pharmaceutical preparations (or pharmaceutical compositions) which comprise an effective dose of at least one compound of the formula I and/or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier, i.e. one or more pharmaceutically acceptable carrier substances or vehicles and/or additives or excipients.

20 The pharmaceuticals according to the invention can be administered orally, for example in the form of pills, tablets, lacquered tablets, sugar-coated tablets, granules, hard and soft gelatin capsules, aqueous, alcoholic or oily solutions, syrups, emulsions or suspensions, or rectally, for example in the form of suppositories. Administration can also be carried out parenterally, for example subcutaneously, intramuscularly or intravenously, in the form of solutions for injection or infusion.

25 Other suitable administration forms are, for example, percutaneous or topical administration, for example in the form of ointments, tinctures, sprays or transdermal therapeutic systems, or the inhalative administration in the form of nasal sprays or aerosol mixtures, or, for example, microcapsules, implants or rods. The preferred administration form depends, among others, on the disease to be treated and on its severity.

30

buffer substances, solvents, solubilizers, agents for achieving a depot effect, salts for altering the osmotic pressure, coating agents or antioxidants.

The dosage of the compound of the formula I to be administered and/or of a

5 pharmaceutically acceptable salt thereof depends on the individual case and is, as is customary, to be adapted to the individual circumstances to achieve an optimum effect. Thus, it depends on the nature and the severity of the disorder to be treated, and also on the sex, age, weight and individual responsiveness of the human or animal to be treated, on the efficacy and duration of action of the compounds used,
10 on whether the use is for the therapy of a acute or chronic disease or prophylactic, or on whether other active compounds are administered in addition to compounds of the formula I. In general, a daily dose of from about 0.01 to about 100 mg/kg, preferably from about 0.1 to about 10 mg/kg, in particular from about 0.3 to about 5 mg/kg (in each case mg per kg of bodyweight) is appropriate for administration to an adult
15 weighing approximately 75 kg in order to obtain the desired results. The daily dose can be administered in a single dose or, in particular when larger amounts are administered, be divided into several, for example two, three or four individual doses. In some cases, depending on the individual response, it may be necessary to deviate upwards or downwards from the given daily dose.

20

The compounds of the formula I can also be used for other purposes than those indicated in the foregoing. Non-limiting examples include diagnostic purposes, the use as biochemical tools and the use as intermediates for the preparation of further compounds, e.g. pharmaceutically active compounds.

25

Examples

HPLC conditions

30 HPLC method a

Column: Daicel Chiralpak AD, 250 x 4.6 mm, 10 μ ; eluent: acetonitrile/isopropanol (120/5) + 0.1 % diethylamine; flow rate: 1.0 ml/min

The amount of a compound of the formula I and/or its pharmaceutically acceptable salts in the pharmaceutical preparations normally ranges from about 0.2 to about 800 mg, preferably from about 0.5 to about 500 mg, in particular from about 1 to about 200 mg, per dose, but depending on the type of the pharmaceutical preparation it may also be higher. The pharmaceutical preparations usually comprise from about 0.5 to about 90 % by weight of the compounds of the formula I and/or their pharmaceutically acceptable salts. The production of the pharmaceutical preparations can be carried out in a manner known per se. To this end, one or more compounds of the formula I and/or their pharmaceutically acceptable salts, together with one or more solid or liquid pharmaceutical carrier substances and/or additives (or auxiliary substances) and, if desired, in combination with other pharmaceutically active compounds having therapeutic or prophylactic action, are brought into a suitable administration form or dosage form which can then be used as a pharmaceutical in human or veterinary medicine.

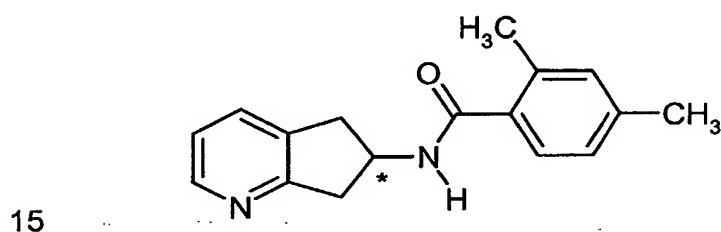
For the production of pills, tablets, sugar-coated tablets and hard gelatin capsules it is possible to use, for example, lactose, starch, for example maize starch, or starch derivatives, talc, stearic acid or its salts, etc. Soft gelatin capsules and suppositories can comprise, for example, fats, waxes, semisolid and liquid polyols, natural or hardened oils, etc. Suitable carrier substances or vehicles for the preparation of solutions, for example of solutions for injection, or of emulsions or syrups are, for example, water, physiologically sodium chloride solution, alcohols such as ethanol, glycerol, polyols, sucrose, invert sugar, glucose, mannitol, vegetable oils, etc. It is also possible to lyophilize the compounds of the formula I and their pharmaceutically acceptable salts and to use the resulting lyophilisates, for example, for preparing preparations for injection or infusion. Suitable carriers for microcapsules, implants or rods are, for example, copolymers of glycolic acid and lactic acid.

Besides the compound or compounds of the invention and carrier substances, the pharmaceutical preparations can also contain additives such as, for example, fillers, disintegrants, binders, lubricants, wetting agents, stabilizers, emulsifiers, dispersants, preservatives, sweeteners, colorants, flavorings, aromatizers, thickeners, diluents,

General acylation method B: To 0.4 mmol of the respective carboxylic acid dissolved in 5 ml of tetrahydrofuran were given 144 mg (0.44 mmol) of O-((cyano(ethoxycarbonyl)methylene)amino)-N,N,N',N'-tetramethyluronium tetrafluoroborate (TOTU) in 1 ml of dimethylformamide and 114 mg (0.88 mmol) of ethyldiisopropylamine. After stirring
 5 at room temperature for 30 min, 0.37 mmol of the respective amine were added and the mixture was stirred for 12 h. The reaction mixture was poured onto a saturated sodium hydrogencarbonate solution, extracted with ethyl acetate and the organic solution dried and concentrated. The residue was purified by preparative HPLC (RP18, acetonitrile/water + trifluoroacetic acid) or by silica gel flash chromatography
 10 (methylene chloride or methylene chloride/methanol).

Example 1

N-(6,7-Dihydro-5H-[1]pyrindin-6-yl)-2,4-dimethylbenzamide (Enantiomer 1)



a) 7-Benzylidene-6,7-dihydro-5H-[1]pyrindine

15 g (0.125 mol) of 6,7-dihydro-5H-[1]pyrindine, 20.1 g (0.19 mol) of freshly distilled benzaldehyde and 24.5 g (0.24 mol) of acetic acid anhydride were heated under
 20 reflux for 24 h. The reaction mixture was evaporated, the residual oil dissolved in methylene chloride, the solution extracted with 1N NaOH solution, and the organic phase dried and evaporated. The residue was distilled under reduced pressure to give 19.3 g (75%) of the title compound.

Boiling point (0.013 mbar): 150°C. Melting point: 72°C.

25

b) 5,6-Dihydro-[1]pyrindin-7-one

19.3 g (0.09 mol) of the compound of step a were dissolved in 250 ml of dry methanol, cooled to -35°C and ozonized for 3 h. 10.56 g (0.17 mol) of dimethylsulfide

HPLC method b

Column: Merck Porospher, 55 x 2 mm, 5 μ ; eluent A: water + 0.05 % trifluoroacetic acid, eluent B: acetonitrile; gradient: from 95 % eluent A / 5 % eluent B to 5 % eluent A / 95 % eluent B in 4 min, 5 % eluent A / 95 % eluent B for 1.5 min; flow rate: 0.5 ml/min

HPLC method c

Column: YMC J'Sphere ODS H80, 33 x 2 mm, 3 μ ; eluent A: water + 0.05 % trifluoroacetic acid), eluent B: acetonitrile; gradient: from 90 % eluent A / 10 % eluent B to 5 % eluent A / 95 % eluent B in 2.5 min, 5 % eluent A / 95 % eluent B for 0.8 min; flow rate: 1.0 ml/min

HPLC method d

Column: Daicel Chiralpak AD, 250 x 4.6 mm, 10 μ ; eluent: n-heptane/isopropanol (10/1); flow rate: 1.0 ml/min

HPLC retention times (RT) are given in minutes.

20

General methods for the acylation of heteroaryl-condensed cycloalkenylamines

General acylation method A: 2.5 mmol of the respective amine were mixed with 550 mg of triethylamine and 5 ml of dioxane or tetrahydrofuran, and 2.5 mmol of the respective carboxylic acid chloride were added. The mixture was stirred at room temperature for 2 h and then poured onto a saturated sodium hydrogencarbonate solution. The mixture was extracted with ethyl acetate and the organic solution dried and concentrated. The residue was purified by preparative HPLC (RP18; acetonitrile/water + trifluoroacetic acid) or by silica gel flash chromatography (methylene chloride or methylene chloride/methanol).

HPLC: RT = 6.40 min (method a).

Enantiomer 2

HPLC: RT = 8.16 min (method a).

5

e) 6,7-Dihydro-5H-[1]pyrindin-6-ylamine (Enantiomer 1 and Enantiomer 2)

The separated enantiomers of N-(6,7-dihydro-5H-[1]pyrindin-6-yl)acetamide were hydrolyzed by heating with 20 ml of 6N HCl in a sealed vessel to 150°C for 4 h.

Evaporation, treatment with an excess of 1N NaOH solution, extraction with ethyl acetate and drying and evaporation of the extracts yielded the two enantiomeric 6,7-dihydro-5H-[1]pyrindin-6-ylamines in a yield of 0.7 g and 0.8 g, respectively.

Enantiomer 1

MS: $m/e = 135$ (M+H)⁺. HPLC: RT = 0.13 (method c).

15

Enantiomer 2

MS: $m/e = 135$ (M+H)⁺. HPLC: RT = 0.13 (method c).

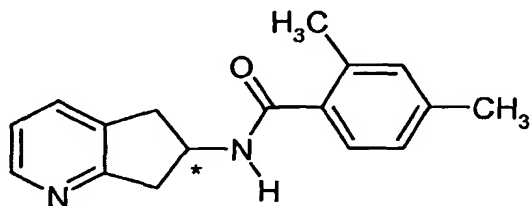
f) N-(6,7-Dihydro-5H-[1]pyrindin-6-yl)-2,4-dimethylbenzamide (Enantiomer 1)

20 The title compound was prepared from chiral dihydro-5H-[1]pyrindin-6-ylamine of step e) according to general acylation method A.

MS: $m/e = 267$ (M+H)⁺. HPLC: RT = 1.12 min (method c).

Example 2

25 N-(6,7-Dihydro-5H-[1]pyrindin-6-yl)-2,4-dimethylbenzamide (Enantiomer 2)



were added, and the reaction mixture was allowed to warm to room temperature overnight. Evaporation and subsequent distillation of the residual oil under reduced pressure gave 6.6 g of the title compound.

Boiling point (0.003 mbar): 150°C.

5

c) 5H-[1]Pyridine-6,7-dione 6-oxime

6.6 g (49.6 mmol) of the compound of step b and 6.97 g (59.5 mmol) of isoamyl nitrite were dissolved in 150 ml of methanol warmed to 45°C and treated dropwise with 8 ml of concentrated hydrochloric acid. After stirring at 45°C for 3 h, the mixture
10 was cooled to 0°C and the precipitated product collected by suction. Yield: 7.3 g (91%).

DC: R_f = 0.2 (silica gel, methylene chloride/methanol (95/5)).

d) N-(6,7-Dihydro-5H-[1]pyrindin-6-yl)acetamide

15 18 g (0.11 mol) of the compound of step c were dissolved in 500 ml of acetic acid and 500 ml of acetic acid anhydride and hydrogenated for 20 h at a pressure of 2 bar over 5 g of palladium on barium sulfate. The reaction mixture was filtered and evaporated. The residue was dissolved in 1000 ml of ethanol, treated with 10.8 ml of perchloric acid and hydrogenated for 10 h at 50°C and a pressure of 3.5 bar over 5 g
20 of palladium on charcoal (10%). The resulting mixture was evaporated, the residue taken up in dilute NaOH solution and extracted with ethyl acetate. Evaporation of the combined organic phases and subsequent chromatography of the residue yielded racemic N-(6,7-dihydro-5H-[1]pyrindin-6-yl)acetamide.

DC: R_f = 0.28 (silica gel, methylene chloride/methanol (9/1)).

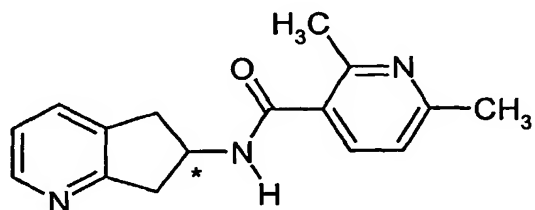
25

The racemic acetamide was separated into the enantiomers by chromatography on a chiral phase (Chiralpak AD; eluent: acetonitrile/isopropanol (120/5) + 0.1 % diethylamine). The yield of enantiomer 1 of N-(6,7-dihydro-5H-[1]pyrindin-6-yl)acetamide was 1.89 g, the yield of enantiomer 2 of N-(6,7-dihydro-5H-[1]pyrindin-
30 6-yl)acetamide was 1.53 g.

Enantiomer 1

Example 5

N-(6,7-Dihydro-5H-[1]pyrindin-6-yl)-2,6-dimethylnicotinamide (Enantiomer 1)



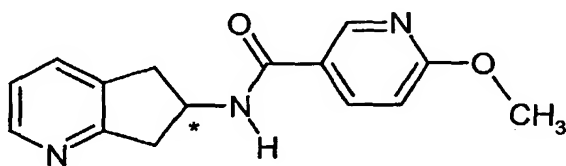
5

The title compound was prepared from chiral 6,7-dihydro-5H-[1]pyrindin-6-ylamine of Example 1, step e, according to general acylation method A.

MS: $m/e = 268$ ($M+H$)⁺. HPLC: RT = 0.15 min (method c).

10 Example 6

N-(6,7-Dihydro-5H-[1]pyrindin-6-yl)-6-methoxynicotinamide (Enantiomer 1)



15 The title compound was prepared from chiral 6,7-dihydro-5H-[1]pyrindin-6-ylamine of Example 1, step e, according to general acylation method A.

MS: $m/e = 270$ ($M+H$)⁺. HPLC: RT = 0.43 min (method c).

Example 7

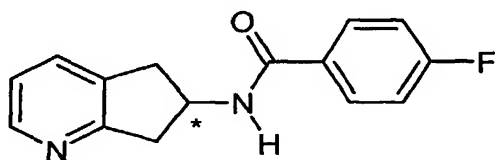
20 2-Methyl-3H-benzimidazole-5-carboxylic acid (6,7-dihydro-5H-[1]pyrindin-6-yl)amide (Enantiomer 1)

The title compound was prepared from chiral 6,7-dihydro-5H-[1]pyrindin-6-ylamine of Example 1, step e), according to general acylation method A.

MS: $m/e = 267$ ($M+H$)⁺. HPLC: RT = 1.12 min (method c).

5 Example 3

N-(6,7-Dihydro-5H-[1]pyrindin-6-yl)-4-fluorobenzamide (Enantiomer 1)

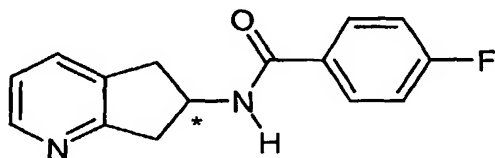


- 10 The title compound was prepared according to general acylation method A, starting from racemic 6,7-dihydro-5H-[1]pyrindin-6-ylamine which had been prepared from the racemic N-(6,7-dihydro-5H-[1]pyrindin-6-yl)acetamide of Example 1, step d, by hydrolysis analogously as described in Example 1, step e, and separation of the racemic N-(6,7-dihydro-5H-[1]pyrindin-6-yl)-4-fluorobenzamide by preparative
- 15 chromatography on a chiral phase (Chiralpak AD; eluent: heptane/isopropanol (10/1). MS: $m/e = 257$ ($M+H$)⁺. HPLC: RT = 15.66 min (method d).

Example 4

N-(6,7-Dihydro-5H-[1]pyrindin-6-yl)-4-fluorobenzamide (Enantiomer 2)

20



The title compound was prepared as described in Example 3 by separation of N-(6,7-dihydro-5H-[1]pyrindin-6-yl)-4-fluorobenzamide.

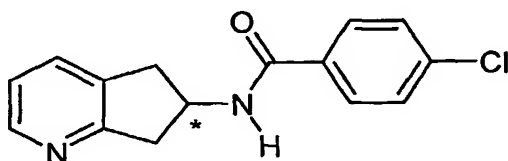
- 25 MS: $m/e = 257$ ($M+H$)⁺. HPLC: RT = 14.96 min (method d)

The title compound was prepared from chiral 6,7-dihydro-5H-[1]pyrindin-6-ylamine of Example 1, step e, according to general acylation method B.

MS: $m/e = 319$ ($M+H$)⁺. HPLC: RT = 1.60 min (method c).

5 Example 10

4-Chloro-N-(6,7-dihydro-5H-[1]pyrindin-6-yl)benzamide (Enantiomer 1), trifluoroacetic acid salt



10

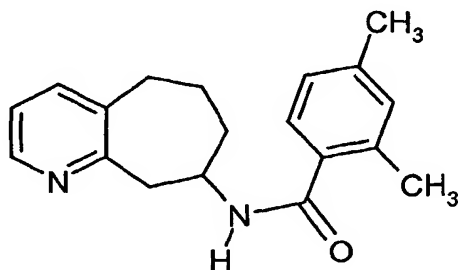
The title compound was prepared from chiral 6,7-dihydro-5H-[1]pyrindin-6-ylamine of Example 1, step e, according to general acylation method A.

MS: $m/e = 273$ ($M+H$)⁺. DC: R_f = 0.29 (silica gel, methylene chloride/methanol (95/5)).

15

Example 11

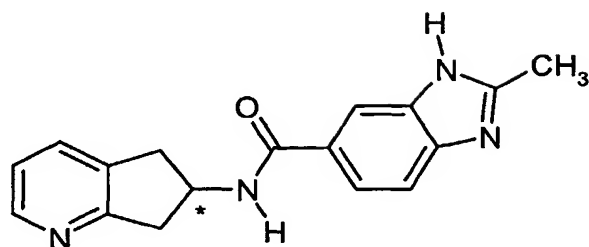
2,4-Dimethyl-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)benzamide



20

a) 9-Benzylidene-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine

The title compound was prepared from 6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridine analogously as described in Example 1, step a. The raw material was purified by silica gel chromatography using methylene chloride as eluent.

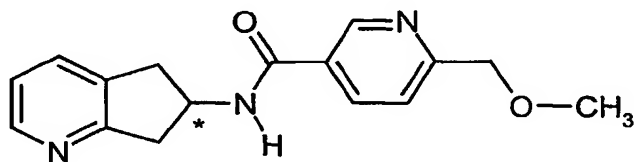


The title compound was prepared from chiral 6,7-dihydro-5H-[1]pyrindin-6-ylamine of Example 1, step e, according to general acylation method A.

5 MS: $m/e = 293 (M+H)^+$. HPLC: RT = 0.17 min (method c).

Example 8

N-(6,7-Dihydro-5H-[1]pyrindin-6-yl)-6-methoxymethylnicotinamide (Enantiomer 1)



10

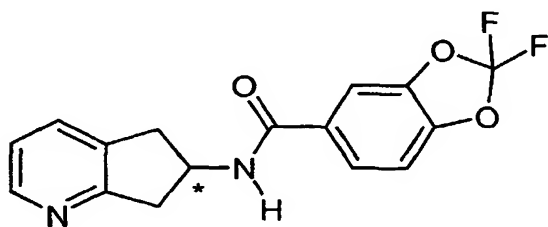
The title compound was prepared from chiral 6,7-dihydro-5H-[1]pyrindin-6-ylamine of Example 1, step e, according to general acylation method B.

MS: $m/e = 284 (M+H)^+$. HPLC: RT = 1.77 min (method b).

15

Example 9

2,2-Difluorobenzo[1,3]dioxole-5-carboxylic acid (6,7-dihydro-5H-[1]pyrindin-6-yl)amide (Enantiomer 1), trifluoroacetic acid salt



20

MS: $m/e = 236 (M+H)^+$. DC: $R_f = 0.47$ (silica gel, n-heptane/ethyl acetate (3/2)).

b) 5,6,7,8-Tetrahydrocyclohepta[b]pyridin-9-one

The title compound was prepared from the compound of step a analogously as described in Example 1, step b. The raw material was purified by silica gel

MS: $m/e = 162 (M+H)^+$. DC: $R_f = 0.72$ (silica gel, methylene chloride/methanol (98/2)).

c) 6,7-Dihydro-5H-cyclohepta[b]pyridine-8,9-dione 8-oxime

6.7 g (41.6 mmol) of the compound of step b were dissolved in 300 ml of diethyl ether and treated with 10 ml of a saturated solution of hydrogen chloride in diethyl ether. To the resulting slurry were added 5.38 g (45.8 mmol) of isoamyl nitrite in 500 ml of tetrahydrofuran and once more 10 ml of a saturated solution of hydrogen chloride in diethyl ether. The mixture was refluxed for 3 h, cooled in an ice bath and the precipitated product isolated by suction. Yield 7.9 g (100%).

MS: $m/e = 191 (M+H)^+$. $R_f = 0.20$ (silica gel, methylene chloride/methanol (98/2)).

d) 6,7,8,9-Tetrahydro-5H-cyclohepta[b]pyridin-8-ylamine

The title compound was prepared from the compound of step c analogously as described in Example 1, steps d and e. The raw material was purified by silica gel chromatography using methylene chloride/methanol (98/2) as eluent.

MS: $m/e = 163 (M+H)^+$. $R_f = 0.09$ (silica gel, methylene chloride/methanol (7/3)).

e) 2,4-Dimethyl-N-(6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-8-yl)benzamide

The title compound was prepared from the compound of step d according to general acylation method A.

MS: $m/e = 295 (M+H)^+$. HPLC: $RT = 3.68$ min (method b).

30

Measurement of activation of eNOS transcription

Activation of eNOS transcription was measured as described in detail in Li et al., "Activation of protein kinase C alpha and/or epsilon enhances transcription of the human endothelial nitric oxide synthase gene", Mol. Pharmacol. 53 (1998) 630.

5 Briefly, a 3.5kB long fragment 5' of the starting codon of the eNOS gene was cloned, sequenced and cloned in firefly luciferase expression plasmids to monitor activation of the eNOS promoter by reporter gene activity. A human endothelial cell line stable transfected and expressing this promoter-reporter construct was used for compound testing. Cells were incubated for 18 h with compounds.

10

All compounds were dissolved in sterile DMSO. A final concentration of 0.5% DMSO in complete medium was allowed. Induction of reporter gene expression in these cells was measured using a standard luciferase assay system (Promega, Cat. No E150) according to the manufacturer's instructions. Luciferase induction in cells

15 incubated with compounds were compared to those incubated with solvent alone.

The ratio of both activities (transcription induction ratio, TIR) was plotted as a function of compound concentration. Typically, TIR values started at low concentrations at a ratio of 1, indicating no compound effect, and extended up to a maximum TIR value TIR(max) which indicates the increase of the eNOS transcription. EC₅₀ values of

20 transcription induction ratios as a function of compound concentration were determined graphically.

The effect of compounds on eNOS-transcription was confirmed in a second assay based on eNOS protein detection. Primary human umbilical vein cord endothelial

25 cells (HUVEC) were isolated and cultivated according to standard procedures.

Confluent cells were incubated with compounds for 18 h and the effect on eNOS protein expression determined by a quantitative Western blotting procedure. After compounds incubation, HUVEC were lysed in ice-cold lysis buffer containing 10mM Tris-HCl, pH 8.0, 1% SDS and protease inhibitors. The lysate was subjected to a

30 standard denaturing polyacrylamide gel electrophoresis and blotted to

nitrocellulose membranes. Using a specific primary monoclonal antibody (Transduction Laboratories, UK) and alkaline phosphatase labelled secondary

antibody (Jackson Labs), a specific eNOS protein band was visualized and quantified based on a chemifluorescence detection method.

The results are shown in the Table below.

5

Compound of example no.	EC ₅₀ (μM)
1	0.079
2	1.1
3	14
4	3.4
5	3.3
6	12
7	23
8	30
9	0.93
10	0.80
11	0.064

The effect of the compounds of the invention can also be investigated in the following animal models (animal experiments are performed in accordance to the German
10 animal protection law and to the guidelines for the use of experimental animals as given by the Guide for the Care and Use of Laboratory Animals of the US National Institutes of Health).

Animals and Treatment (Experiments A - C)

15

ApoE and eNOS deficient mice (C57BL/6J background, Jackson Laboratory, Bar Harbor, Me) are used. All animals are 10 – 12 weeks of age and weigh 22 to 28 g. Three days before surgery mice are divided into 4 groups (apoE control, n=10-12; apoE with test compounds, n=10-12; eNOS control, n=10-12; eNOS with test

compounds, n=10-12) and receive either a standard rodent chow (containing 4 % fat and 0.001 % cholesterol; in the following designated as placebo group) or a standard rodent chow + test compound (10 or 30 mg/kg/d p.o.).

5 A. Anti-hypertensive effect in ApoE knockout mice

Blood-pressure is determined in conscious mice using a computerized tail-cuff system (Visitech Systems, Apex, Nc). After treatment of ApoE deficient mice and eNOS deficient mice with the test compounds the blood pressure is compared to the
10 results obtained with a placebo treatment.

B. Inhibition of neointima formation and atherogenesis (femoral artery cuff)

After 3 day treatment of ApoE deficient mice with the respective compound,
15 (10mg/kg/d pressed in chow), animals are anesthetized with an intraperitoneal injection of pentobarbital (60 mg/kg) followed by an intramuscular injection of xylazine (2 mg/kg) and a cuff is placed around the femoral artery as described in Moroi et al.(J. Clin. Invest. 101 (1998) 1225). Briefly, the left femoral artery is dissected. A non-occlusive 2.0 mm polyethylene cuff made of PE-50 tubing (inner diameter 0.56
20 mm, outer diameter 0.965 mm, Becton Dickinson, Mountain View, Ca) is placed around the artery and tied in place with two 7-0 sutures. The right femoral artery is isolated from the surrounding tissues but a cuff is not placed. Treatment with the respective compound is continued for 14 days after surgery. Then the animals are sacrificed. The aorta are taken for determination of vascular eNOS expressions by
25 quantitative western blotting. Both femoral arteries are harvested, fixed in formalin and embedded in paraffin. 20 cross sections (10 μ m) are cut from the cuffed portion of the left femoral artery and from the corresponding segment of the right artery. Sections are subjected to standard hematoxylin and eosin staining. Morphometric analyses are performed using an image analysis computer program (LeicaQWin,
30 Leica Imaging Systems, Cambridge, GB). For each cross section the area of the lumen, the neointima and the media are determined. To this end, the neointima is defined as the area between the lumen and the internal elastic lamina and the media

is defined as the area between the internal and the external elastic lamina. The ratio between the area of the neointima and the area of the media is expressed as the neointima/media ratio. The results obtained in the compound group are compared to those obtained in the placebo group.

5

C. Prevention of atherosclerotic plaque formation in chronic treatment

ApoE deficient mice are treated for 16 weeks with the respective compound pressed in chow and finally sacrificed. Aortas are removed from each mouse, fixed in formalin and embedded in paraffin. Plaque formation is measured via lipid lesions formation in the aortas (from aortic arch to diaphragm) and is analyzed by oil red O staining. For quantifying the effect of the respective compound on vascular eNOS expression the femoral arteries are used in this experiment. The results obtained in the compound group are compared to those obtained in the placebo group.

15

D. Improvement of coronary function in diseased ApoE deficient mice

Old Male wild-type C57BL/6J mice (Charles River Wiga GmbH, Sulzfeld), and apoE deficient mice (C57BL/6J background, Jackson Laboratory, Bar Harbor, Me) 6 month of age and weighing 28 to 36 g are used in the experiments. Mice are divided into 3 groups (C57BL/6, n=8; apoE control, n=8; apoE with respective compound, n=8) and receive for 8 weeks either a standard rodent chow (containing 4 % fat and 0.001 % cholesterol) or a standard rodent chow + respective compound (30 mg/kg/d p.o.). Mice are anesthetized with sodium pentobarbitone (100 mg/kg i.p.), and the hearts are rapidly excised and placed into ice-cold perfusion buffer. The aorta is cannulated and connected to a perfusion apparatus (Hugo Sachs Electronics, Freiburg, Germany) which is started immediately at a constant perfusion pressure of 60 mm Hg. Hearts are perfused in a retrograde fashion with modified Krebs bicarbonate buffer, equilibrated with 95% O₂ and 5% CO₂ and maintained at 37.5°C.

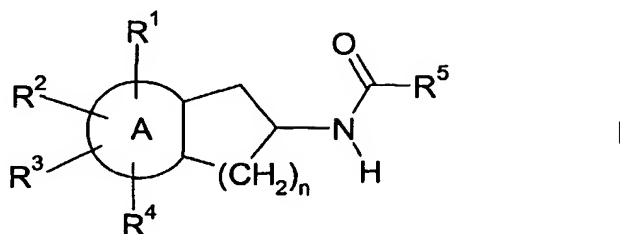
A beveled small tube (PE 50) is passed through a pulmonary vein into the left ventricle and pulled through the ventricular wall, anchored in the apex by a fluted end, and connected to a tip-micromanometer (Millar 1.4 French). The left atrium is

cannulated through the same pulmonary vein and the heart switched to the working mode with a constant preload pressure of 10 mm Hg and an afterload pressure of 60 mm Hg. Aortic outflow and atrial inflow are continuously measured using ultrasonic flow probes (HSE/Transonic Systems Inc.). Coronary flow is calculated as the difference between atrial flow and aortic flow. All hemodynamic data are digitized at a sampling rate of 1000 Hz and recorded with a PC using specialized software (HEM, Notocord).

Hearts are allowed to stabilize for 30 min. All functional hemodynamic data are measured during steady state, and during volume- and pressure loading. Left ventricular function curves are constructed by varying pre-load pressure. For acquisition of preload curves, afterload is set at 60 mm Hg and preload is adjusted in 5 mm Hg steps over a range of 5 to 25 mm Hg. Hearts are allowed to stabilize at baseline conditions between pressure- and volume-loading.

Patent Claims

1. A compound of the formula I,



5

in any of its stereoisomeric forms or a mixture thereof in any ratio, or a pharmaceutically acceptable salt thereof, wherein in the formula I:

- 10 the ring A, which comprises the two carbon atoms common to the ring A and the cycloalkenyl ring in formula I, is an aromatic 5-membered or 6-membered ring containing 1 or 2 nitrogen atoms as ring heteroatoms, or an aromatic 5-membered ring containing 1 ring heteroatom which is an oxygen atom or a sulfur atom or 2 ring heteroatoms one of which is a nitrogen atom and the other of which is an oxygen
- 15 atom or a sulfur atom;

- R¹ and R⁴ are independently from each other selected from the group consisting of: H; unsubstituted and at least monosubstituted C₁-C₁₀-alkyl, C₂-C₁₀-alkenyl and C₂-C₁₀-alkynyl, the substituents of which are selected from the group consisting of F, OH, C₁-C₈-alkoxy, C₁-C₈-alkylmercapto, -CN, COOR⁶, CONR⁷R⁸, and unsubstituted
- 20 and at least monosubstituted phenyl and heteroaryl where the substituents of the phenyl and heteroaryl groups are selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃; unsubstituted and at least monosubstituted phenyl and heteroaryl the substituents of which are selected from the group
- 25 consisting of halogens, -CN, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃; COR⁹; CONR¹⁰R¹¹; COOR¹²; CF₃; halogens; -CN; NR¹³R¹⁴; OR¹⁵; S(O)_mR¹⁶; SO₂NR¹⁷R¹⁸; and NO₂; but cannot be halogen, -CN or NO₂ if R¹ or R⁴ is bonded to a ring nitrogen atom;

- R^2 and R^3 are independently from each other selected from the group consisting of: H; halogens; -CN; unsubstituted and at least monosubstituted C_1 - C_{10} -alkyl the substituents of which are selected from the group consisting of OH, phenyl, and heteroaryl; OH; C_1 - C_{10} -alkoxy; phenoxy; $S(O)_mR^{19}$; CF_3 ; -CN; NO_2 ; C_1 - C_{10} -alkylamino; di(C_1 - C_{10} -alkyl)amino; (C_1 - C_6 -alkyl)-CONH-; unsubstituted and at least monosubstituted phenyl-CONH- and phenyl-SO₂-O- the substituents of which are selected from the group consisting of halogens, -CN, methyl and methoxy; C_1 - C_6 -alkyl-SO₂-O-; unsubstituted and at least monosubstituted (C_1 - C_6 -alkyl)-CO- the substituents of which are selected from the group consisting of F, di(C_1 - C_3 -alkyl)amino, pyrrolidinyl and piperidinyl; and phenyl-CO- the phenyl part of which is unsubstituted or at least monosubstituted by substituents selected from the group consisting of C_1 - C_3 -alkyl, halogens and methoxy; but cannot be halogen, -CN or NO_2 if R^2 or R^3 is bonded to a ring nitrogen atom;
- where, if A is a 6-membered aromatic ring, 2 or 3 of the groups R^1 , R^2 , R^3 and R^4 are present and are bonded to the carbon atoms in the ring A which are not shared with the cycloalkenyl ring, and, if A is a 5-membered aromatic ring, 1, 2 or 3 of the groups R^1 , R^2 , R^3 and R^4 are present and are bonded to the carbon atoms in the ring A which are not shared with the cycloalkenyl ring and, in the case of a pyrrole, pyrazole or imidazole ring, to 1 ring nitrogen atom;

- R^5 is a group Ar or a group Heter both of which are unsubstituted or carry one or more identical or different substituents selected from the group consisting of: halogens; -CN; NH_2 ; unsubstituted and at least monosubstituted C_1 - C_{10} -alkyl, C_2 - C_{10} -alkenyl, C_2 - C_{10} -alkynyl, C_1 - C_{10} -alkoxy, C_1 - C_{10} -alkylamino and di(C_1 - C_{10} -alkyl)amino, the substituents of which are selected from the group consisting of F, OH, C_1 - C_8 -alkoxy, aryloxy, C_1 - C_8 -alkylmercapto, NH_2 , C_1 - C_8 -alkylamino and di(C_1 - C_8 -alkyl)amino; C_3 - C_5 -alkandiyl; phenyl; heteroaryl; aryl-substituted or heteroaryl-substituted C_1 - C_4 -alkyl; CF_3 ; NO_2 ; OH; phenoxy; benzyloxy; (C_1 - C_{10} -alkyl)-COO-; $S(O)_mR^{20}$; SH; phenylamino; benzylamino; (C_1 - C_{10} -alkyl)-CONH-; (C_1 - C_{10} -alkyl)-CO-N(C_1 - C_4 -alkyl)-; phenyl-CONH-; phenyl-CO-N(C_1 - C_4 -alkyl)-; heteroaryl-CONH-; heteroaryl-CO-N(C_1 - C_4 -alkyl)-; (C_1 - C_{10} -alkyl)-CO-; phenyl-CO-; heteroaryl-CO-;

CF₃-CO-; -OCH₂O-; -OCF₂O-; -OCH₂CH₂O-; -CH₂CH₂O-; COOR²¹; CONR²²R²³; C(NH)-NH₂; SO₂NR²⁴R²⁵; R²⁶SO₂NH-; R²⁷SO₂N(C₁-C₆-alkyl)-; and a residue of a saturated or at least monounsaturated aliphatic, monocyclic 5-membered to 7-

- 5 consisting of N, O and S, which heterocycle can be substituted by one or more substituents selected from the group consisting of halogens, C₁-C₃-alkyl, C₁-C₃-alkoxy, OH, oxo and CF₃, where said heterocycle can optionally be condensed to the said group Ar or the said group Hetar; wherein all aryl, heteroaryl, phenyl, aryl-containing, heteroaryl-containing and phenyl-containing groups, which are optionally
- 10 present in the said substituents of the said group Ar or the said group Hetar, can be substituted by one or more substituents selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, OH, C₁-C₃-alkoxy, and CF₃;

R⁶ is selected from the group consisting of:

- 15 H; C₁-C₁₀-alkyl which can be substituted by one or more substituents selected from the group consisting of F, C₁-C₈-alkoxy and di(C₁-C₈-alkyl)amino; aryl-(C₁-C₄-alkyl)- and heteroaryl-(C₁-C₄-alkyl)- both of which can be substituted by one or more substituents selected from the group consisting of halogens, C₁-C₄-alkyl, C₁-C₄-alkoxy and di(C₁-C₆-alkyl)amino;

20

R⁷ is selected from the group consisting of:

- H; C₁-C₁₀-alkyl which can be substituted by one or more substituents selected from the group consisting of F, C₁-C₈-alkoxy, di(C₁-C₈-alkyl)amino and phenyl; phenyl; indanyl; and heteroaryl; wherein each of the aromatic groups can be unsubstituted or
- 25 carry one or more substituents selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃;

R⁸ is H or C₁-C₁₀-alkyl;

- 30 R⁹ is selected from the group consisting of:

C₁-C₁₀-alkyl which can be substituted by one or more substituents from the group consisting of F, C₁-C₄-alkoxy and di(C₁-C₃-alkyl)amino; and unsubstituted and at

least monosubstituted phenyl and heteroaryl the substituents of which are selected from the group consisting of C₁-C₃-alkyl, C₁-C₃-alkoxy, halogens, -CN and CF₃;

R¹⁰, independently from R⁷, is defined as R⁷;

5

R¹¹, independently from R⁸, is defined as R⁸;

R¹², independently from R⁶, is defined as R⁶;

10 R¹³ is selected from the group consisting of:

H; C₁-C₆-alkyl; unsubstituted and substituted phenyl, benzyl, heteroaryl, (C₁-C₆-alkyl)-CO-, phenyl-CO-, and heteroaryl-CO-, the substituents of which are selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃, wherein one or more of these substituents can be present;

15

R¹⁴, independently from R¹³, is defined as R¹³;

R¹⁵ is selected from the group consisting of:

H; C₁-C₁₀-alkyl; (C₁-C₃-alkoxy)-C₁-C₃-alkyl- and substituted and unsubstituted benzyl, phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃, wherein one or more of these substituents can be present;

20

R¹⁶ is selected from the group consisting of:

25 C₁-C₁₀-alkyl which can be substituted by one or more substituents selected from the group consisting of F, OH, C₁-C₈-alkoxy, aryloxy, C₁-C₈-alkylmercapto, C₁-C₈-alkylamino and di(C₁-C₈-alkyl)amino; CF₃; and substituted and unsubstituted phenyl and heteroaryl, the substituents of which are selected from the group consisting of halogens, -CN, C₁-C₃-alkyl, C₁-C₃-alkoxy and CF₃, wherein one or more of these substituents can be present;

30

R¹⁷, independently from R⁷, is defined as R⁷;

R^{18} , independently from R^8 , is defined as R^8 ;

R^{19} , independently from R^{16} , is defined as R^{16} ;

5

R^{20} , independently from R^{16} , is defined as R^{16} ;

R^{21} , independently from R^6 , is defined as R^6 ;

10 R^{22} , independently from R^7 , is defined as R^7 ;

R^{23} , independently from R^8 , is defined as R^8 ;

R^{24} , independently from R^7 , is defined as R^7 ;

15

R^{25} , independently from R^8 , is defined as R^8 ;

R^{26} , independently from R^{16} , is defined as R^{16} ;

20 R^{27} , independently from R^{16} , is defined as R^{16} ;

heteroaryl is a residue of a 5-membered to 10-membered, aromatic, monocyclic or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S;

25

the group Hetar is a residue of a 5-membered to 10-membered, aromatic, monocyclic or bicyclic heterocycle containing one or more heteroatoms selected from the group consisting of N, O and S;

30 aryl is phenyl, naphth-1-yl or naphth-2-yl;

the group Ar is phenyl, naphth-1-yl or naphth-2-yl;

m is 0, 1 or 2;

n is 1, 2 or 3.

5

2. A compound of the formula I as defined in claim 1, in any of its stereoisomeric forms or a mixture thereof in any ratio, or a pharmaceutically acceptable salt thereof, wherein in the formula I the ring A is an aromatic 6-membered ring containing 1 or 2 nitrogen atoms as ring heteroatoms.

10

3. A compound of the formula I as defined in claim 1, in any of its stereoisomeric forms or a mixture thereof in any ratio, or a pharmaceutically acceptable salt thereof, wherein in the formula I the ring A is an aromatic 5-membered ring containing a sulfur atom as ring heteroatom or a sulfur atom and a nitrogen atom as ring heteroatoms.

15

4. A compound of the formula I as defined in one or more of claims 1 to 3, in any of its stereoisomeric forms or a mixture thereof in any ratio, or a pharmaceutically acceptable salt thereof, wherein in the formula I the number n is 1.

20 5. A compound of the formula I as defined in one or more of claims 1 to 3, in any of its stereoisomeric forms or a mixture thereof in any ratio, or a pharmaceutically acceptable salt thereof, wherein in the formula I the number n is 3.

25 6. A compound of the formula I as defined in one or more of claims 1 to 5, in any of its stereoisomeric forms or a mixture thereof in any ratio, or a pharmaceutically acceptable salt thereof, wherein in the formula I the residues R¹ and R⁴ are independently from one another selected from the group consisting of H, C₁-C₄-alkyl and halogens and the residues R² and R³ are independently from one another selected from the group consisting of H, C₁-C₄-alkyl and halogens.

30

7. A compound of the formula I as defined in one or more of claims 1 to 6, in any of its stereoisomeric forms or a mixture thereof in any ratio, or a pharmaceutically acceptable salt thereof, for use as pharmaceutical.

5 8. A pharmaceutical preparation, comprising an effective dose of at least one compound of the formula I as defined in one or more of claims 1 to 6, in any of its stereoisomeric forms or a mixture thereof in any ratio, and/or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

10 9. The use of a compound of the formula I as defined in one or more of claims 1 to 6, in any of its stereoisomeric forms or a mixture thereof in any ratio, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the stimulation of the expression of endothelial NO synthase.

15 10. The use of a compound of the formula I as defined in one or more of claims 1 to 6, in any of its stereoisomeric forms or a mixture thereof in any ratio, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for the treatment of cardiovascular diseases, stable or unstable angina pectoris, coronary heart disease, Prinzmetal angina, acute coronary syndrome, heart failure,
20 myocardial infarction, stroke, thrombosis, peripheral artery occlusive disease, endothelial dysfunction, atherosclerosis, restenosis, endothel damage after PTCA, hypertension, essential hypertension, pulmonary hypertension, secondary hypertension, renovascular hypertension, chronic glomerulonephritis, erectile dysfunction, ventricular arrhythmia, diabetes, diabetes complications, nephropathy,
25 retinopathy, angiogenesis, asthma bronchiale, chronic renal failure, cirrhosis of the liver, osteoporosis, restricted memory performance or a restricted ability to learn, or for the lowering of cardiovascular risk of postmenopausal women or of women taking contraceptives.

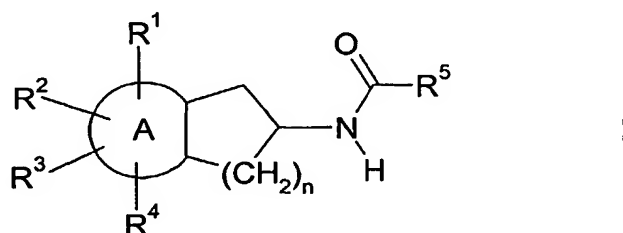
07. Aug. 2002

Abstract

Acylated, heteroaryl-condensed cycloalkenylamines and their use as pharmaceuticals

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The present invention relates to acylated, heteroaryl-condensed cycloalkenylamines of the formula I,



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in which A, R¹, R², R³, R⁴, R⁵ and n have the meanings indicated in the claims. The compounds of formula I are valuable pharmacologically active compounds which are useful in the treatment of various disease states including cardiovascular disorders such as atherosclerosis, thrombosis, coronary artery disease, hypertension and cardiac insufficiency. They upregulate the expression of the enzyme endothelial nitric oxide (NO) synthase and can be applied in conditions in which an increased expression of said enzyme or an increased NO level or the normalization of a decreased NO level is desired. The invention furthermore relates to processes for the preparation of compounds of the formula I, their use, in particular as active ingredients in pharmaceuticals, and pharmaceutical preparations comprising them.

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